DISSERTATION ON

RANDOMISED CONTROLLED TRIAL OF

NEBULISED BUDESONIDE VERSUS ORAL PREDNISOLONE

IN ACUTE SEVERE ASTHMA

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CERTIFICATE

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CONTENTS

Introduction

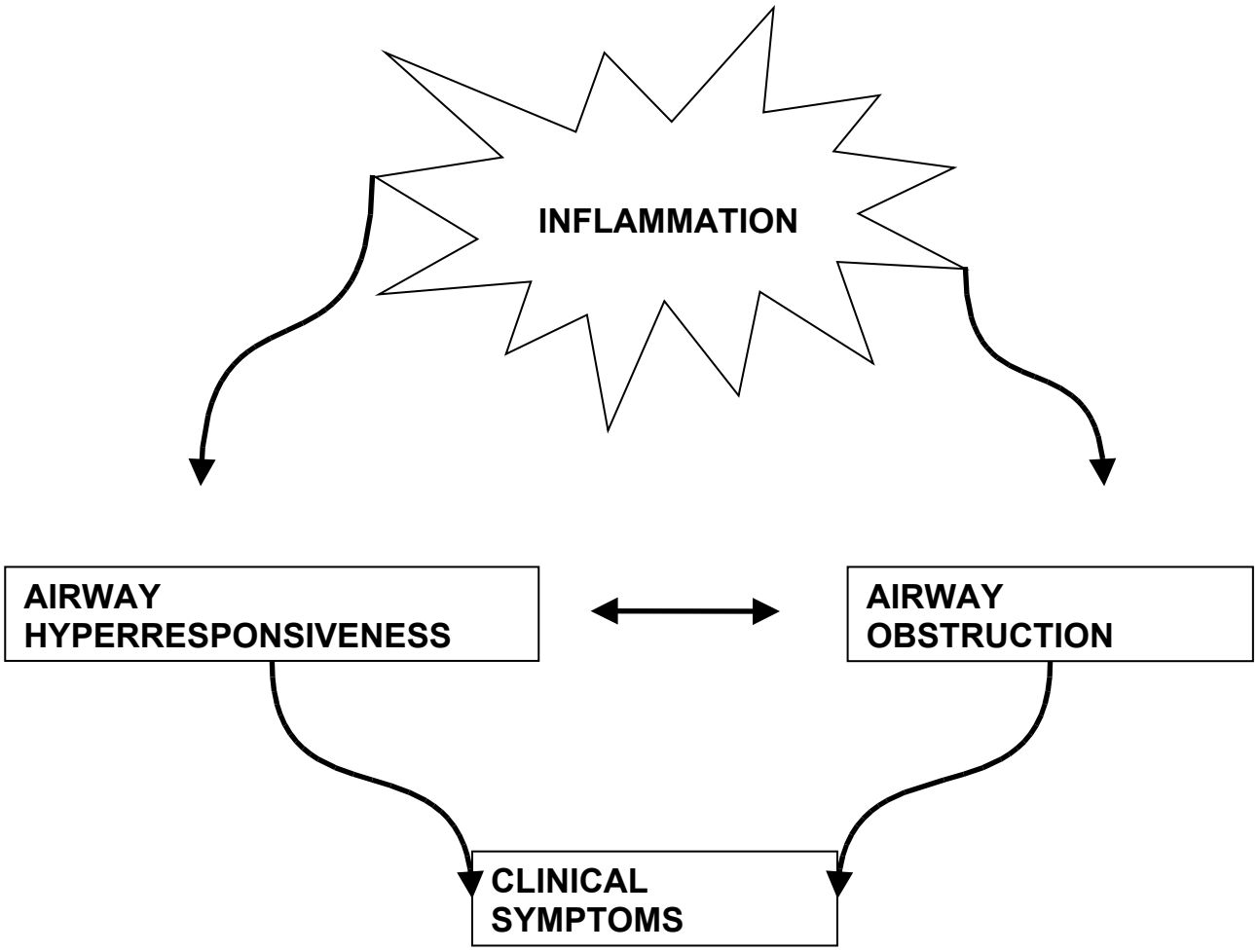
Asthma has been recognized as a disease since the earliest times. In the Corpus Hippocraticum, Hippocrates used the term "ασθμα" to indicate any form of breathing difficulty manifesting itself by panting. Aretaeus of Cappadocia, a well-known Greek physician (second century A.D.), is credited with providing the first detailed description of an asthma attack[1].

DEFINITION[2]

Asthma is a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation. The interaction of these features of asthma determines the clinical manifestations and severity of asthma (figure1) and the response to treatment.

CHARACTERISTICS OF CLI NICAL ASTHMA[2]
• Symptom • Airway obstruction • Inflammation • Hyperresponsiveness

Figure 1 THE INTERPLAY AND INTERACTION BETWEEN AIRWAY INFLAMMATION AND THE CLINICAL SYMPTOMS AND PATHOPHYSIOLOGY OF ASTHMA[2]



EPIDEMIOLOGY[3]

Asthma is one of the most common chronic diseases in the world. It is estimated that around 300 million people in the world currently have asthma. Considerably higher estimates can be obtained with less conservative criteria for the diagnosis of clinical asthma. Asthma has become more common in both children and adults around the world in recent decades.

Globally, childhood asthma prevalence varies widely in different locales. A large international survey study of childhood asthma prevalence in 56 countries (*International Study of Asthma and Allergies in Childhood*) found a wide range in asthma prevalence, from 1.6 to 36.8%. In India, a tenfold variation in the prevalence of childhood asthma has been observed.

There has been a marked increase in the prevalence of asthma in Southern Asia (Bangladesh, Bhutan, India, Nepal, Seychelles, and Sri Lanka) over the last two decades with up to threefold increase in children. The region's industrialisation and urban growth is occurring at an unprecedented rate in what was previously a predominately agrarian society. India is projected to become the world's most populous nation by the year 2050. As a result, further predicted increase in the prevalence of asthma will result in a marked increase in the number of asthmatics. The levels of air pollution in cities in the region are well above the permissible levels recommended by national and international guidelines.

In view of the well documented association between high levels of air pollution and exacerbations of asthma, and the important role of air pollution as a risk factor contributing to respiratory and all-cause mortality, reducing the level of air pollution remains one of the most important public health priorities in Southern Asia. Indoor air pollution remains a major risk factor for respiratory disease, including asthma.

PATHOPHYSIOLOGY AND PATHOGENESIS OF ASTHMA[2]

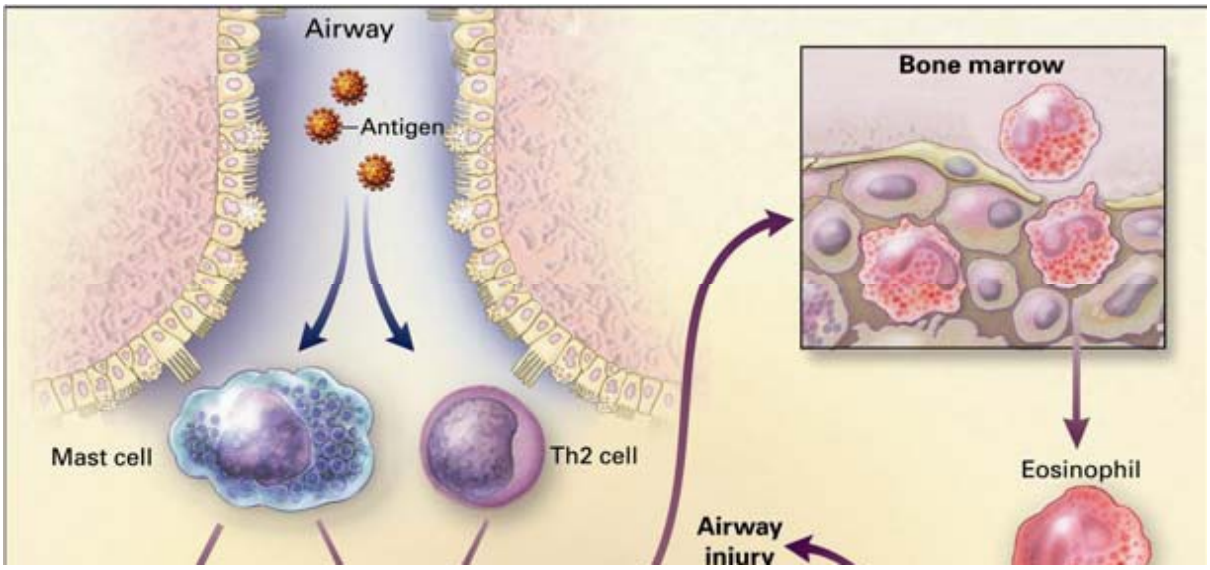
Airflow limitation in asthma is recurrent and caused by a variety of changes in the airway.

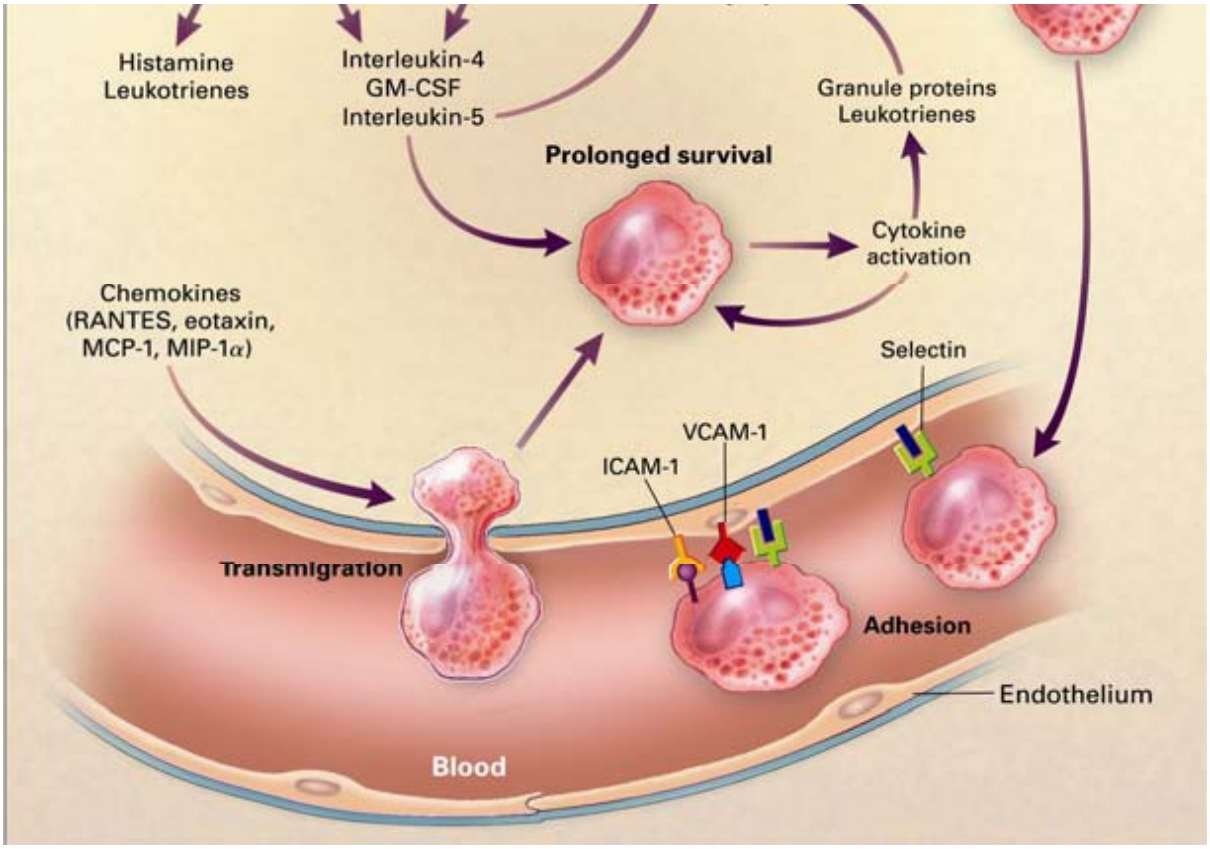
- ✓ Bronchoconstriction
- ✓ Airway edema
- ✓ Airway hyperresponsiveness
- ✓ Airway remodelling

PATHOPHYSIOLOGIC MECHANISMS IN THE DEVELOPMENT OF AIRWAY INFLAMMATION[2]

Inflammation has a central role in the pathophysiology of asthma. As noted in the definition of asthma, airway inflammation involves an interaction of many cell types and multiple mediators with the airways that eventually results in the characteristic pathophysiological features of the disease: *bronchial inflammation* and *airflow limitation* that result in recurrent episodes of cough, wheeze, and shortness of breath. The pattern of airway inflammation in asthma, however, does not necessarily vary depending upon disease severity, persistence, and duration of disease. The cellular profile and the response of the structural cells in asthma are quite consistent.

FIGURE 2 AIRWAY INFLAMMATION[2]





Inhaled antigen activates mast cells and Th2 cells in the airway. They in turn induce the production of mediators of Inflammation (such as histamine and leukotrienes) and cytokines including interleukin-4 and interleukin-5. Interleukin-5 travels to the bone marrow and causes terminal differentiation of eosinophils. Circulating eosinophils enter the area of allergic inflammation and begin migrating to the lung by rolling, through interactions with selectins, and eventually adhering to endothelium through the binding of integrins to members of the immunoglobulin superfamily of adhesion proteins: vascular-cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1). As the eosinophils enter the matrix of the airway through the influence of various chemokines and cytokines, their survival is prolonged by interleukin-4 and granulocyte-macrophage colony-stimulating factor (GM-CSF). On activation, the eosinophil releases inflammatory mediators, such as leukotrienes and granule proteins, to injure airway tissues. In addition, eosinophils can generate GM-CSF to prolong and potentiate their survival and contribution to persistent airway inflammation. MCP-1, monocyte chemotactic protein; and MIP-1α, macrophage inflammatory protein.

PATHOGENESIS[2]

The expression of asthma is a complex, interactive process that depends on the interplay between two major factors—host factors (particularly genetics) and environmental exposures that occur at a crucial time in the development of the immune system.

In summary, our understanding of asthma pathogenesis and underlying mechanisms now includes the concept that gene - environmental interactions are critical factors in the development of airway inflammation and eventual alteration in the pulmonary physiology that is characteristic of clinical asthma[2].

ROLE OF CORTICOSTEROIDS IN MANAGEMENT OF ASTHMA

The NAEPP (National Asthma Education and Prevention Program)[2] guidelines recommend daily Inhaled Corticosteroid therapy as the treatment of choice for all patients with persistent asthma. Inhaled Corticosteroids therapy has been shown to reduce asthma symptoms, improve lung function, reduce AHR (Airway hyperresponsiveness), reduce "rescue" medication use and, most important, reduce urgent care visits, hospitalizations, and prednisolone use for asthma exacerbations by about 50%. Systemic corticosteroids either orally or parenterally has been used in the management of acute exacerbation of asthma. Opposed, inhaled corticosteroids (ICS) have been considered ineffective in treatment of acute exacerbations of asthma. Nevertheless, many studies published in the past 15 yrs have showed therapeutic early effects (after minutes of its administration) suggesting different mechanism of action of topical character (non-genomic).

Inhaled corticosteroids suppress airway inflammation and components of airway

remodelling in bronchial asthma. In the tracheobronchial (airway) vasculature, these include the inhibition of inflammatory hyperperfusion, microvascular hyperpermeability, mucosal oedema formation, and the formation of new blood vessels (angiogenesis). [8]

Corticosteroids are now known to exert their effects on the airway vasculature through genomic and non-genomic mechanisms. Genomic actions involve the regulation of target genes, and suppress most of the vascular elements of inflammation and angiogenesis in the airway. In contrast, non-genomic actions are mediated by rapid cellular mechanisms, and induce transient vasoconstriction in the airway, thereby reversing inflammatory hyperperfusion[8].

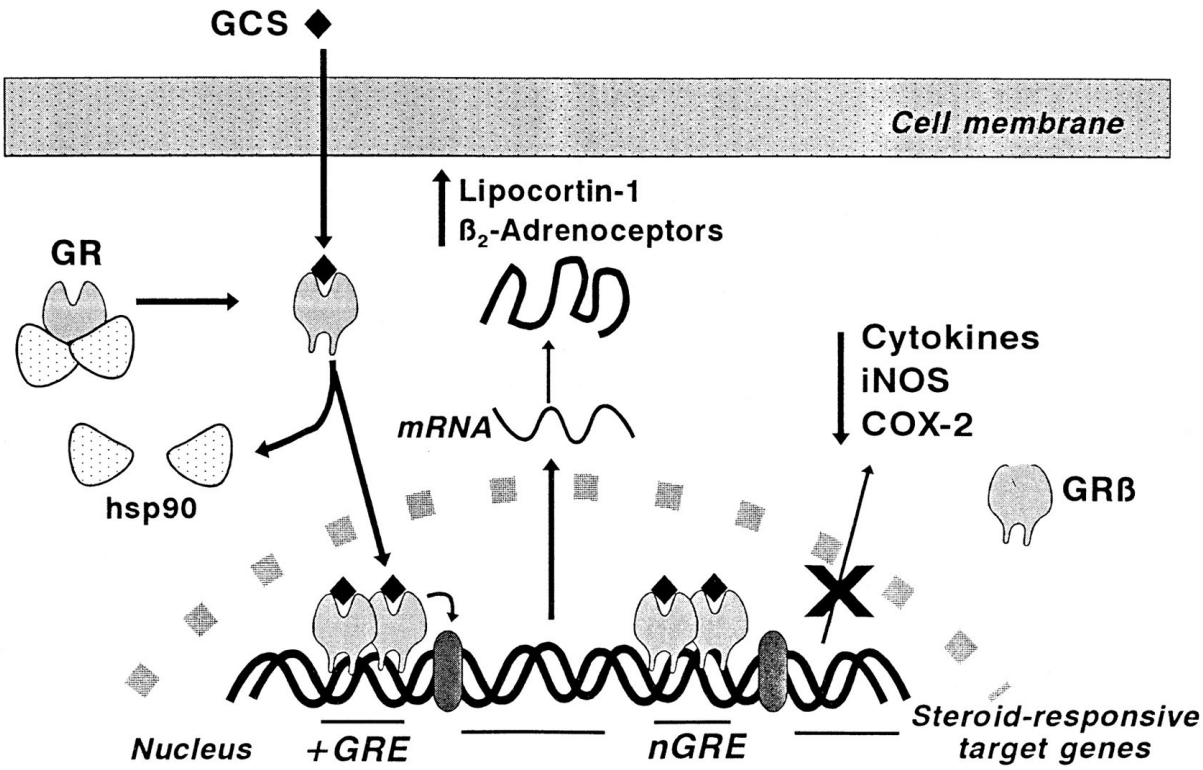
The vascular actions of corticosteroids contribute to controlling clinical symptoms of asthma primarily by influencing airway calibre in the lung periphery and airway hyperreactivity.

GENOMIC EFFECTS OF CORTICOSTEROIDS

Systemic Corticosteroids (SCS) act by reducing airway inflammation. Systemic Corticosteroids require 4 to 24 hrs to improve pulmonary function and reduce hospitalisations[4]. This time delay is due to the proposed mechanism of action of Systemic Corticosteroids i.e. gene transcription and altered protein synthesis (see figure 3). Genomic actions involve the regulation of target genes, and suppress most of the vascular elements of inflammation and angiogenesis in the airway[8]. Corticosteroids increase the synthesis of anti-inflammatory proteins or inhibit the synthesis of many inflammatory

proteins through suppression of the genes that encode them. This genomic effect may take several hours or days.

FIGURE 3 CLASSIC (GENOMIC) MODEL OF GLUCOCORTICOID ACTION[6]



The glucocorticoid enters the cell and binds to a cytoplasmic glucocorticoid receptor (GR) that is complexed with two molecules of a 90-kD heat shock protein (hsp 90)[2]. Glucocorticoid Receptor then translocates to the nucleus where, as a dimer, it binds to a glucocorticoid recognition sequence (GRE) on the 5'-upstream promoter sequence of steroid-responsive genes. GREs may increase transcription and nGREs may decrease transcription, resulting in increased or decreased messenger RNA (mRNA) and protein synthesis.

RAPID NON-GENOMIC EFFECTS OF CORTICOSTEROIDS[4]

Although the major anti-inflammatory effects of corticosteroids are due to transcriptional mechanisms, evidence is growing for actions manifested within seconds or minutes. These effects are mediated by cellular mechanisms that are too rapid to involve gene expression and have been termed

non-genomic actions. Non-genomic actions are initiated by specific interactions with membrane-bound or Cytoplasmic GRs (Glucocorticoid receptors), or nonspecific interactions with the cell membrane[8].

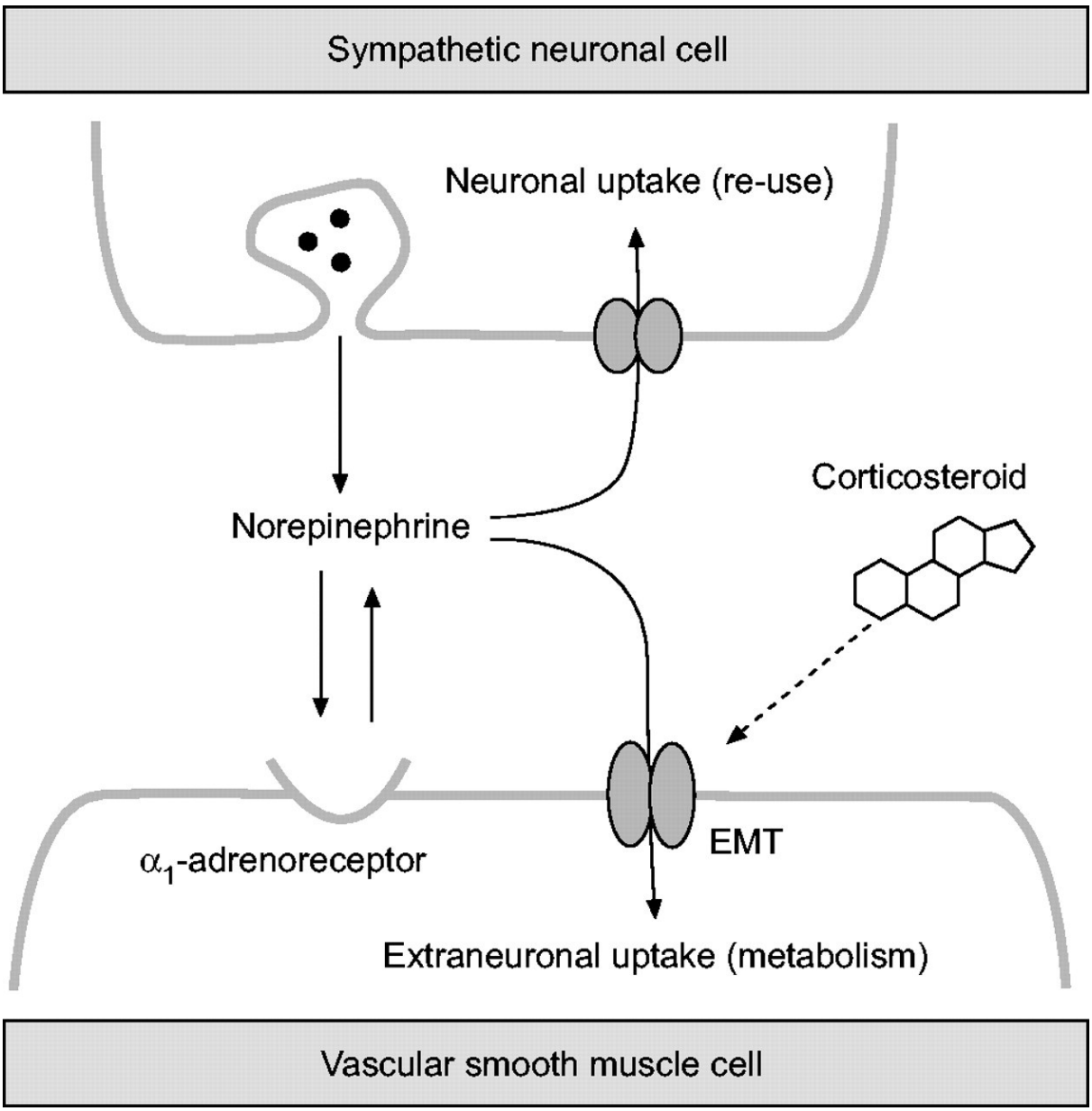
Most recently research has been focussed on these rapid non-genomic effects of Inhaled Corticosteroids (ICS) on airway smooth muscle tone and in decreasing airway blood flow by altering vascular tone. Asthmatics show a significant increase in mucosal blood flow compared with healthy subjects. Inhalation of corticosteroids decreases airway blood flow by modulating sympathetic control of vascular tone. Corticosteroids inhibit the uptake of norepinephrine thereby increasing norepinephrine concentration at the neuromuscular junction hence inducing vasoconstriction (see figure 4). This enhances the action of inhaled bronchodilators by diminishing their clearance from the airways. Thus simultaneous administration of Inhaled Corticosteroids and bronchodilators results in greater effects.

In summary corticosteroids show two different effects on acute asthma patients (see figure 5),

1. the classical *anti-inflammatory or genomic action* , involving modification of gene expression, that occurs with a time lag of hours or days

2. the *non-genomic action* with a rapid onset (minutes), is reversible (short duration) and is dose-dependent.

FIGURE 4 RAPID NON – GENOMIC ACTION OF CORTICOSTEROIDS[8]

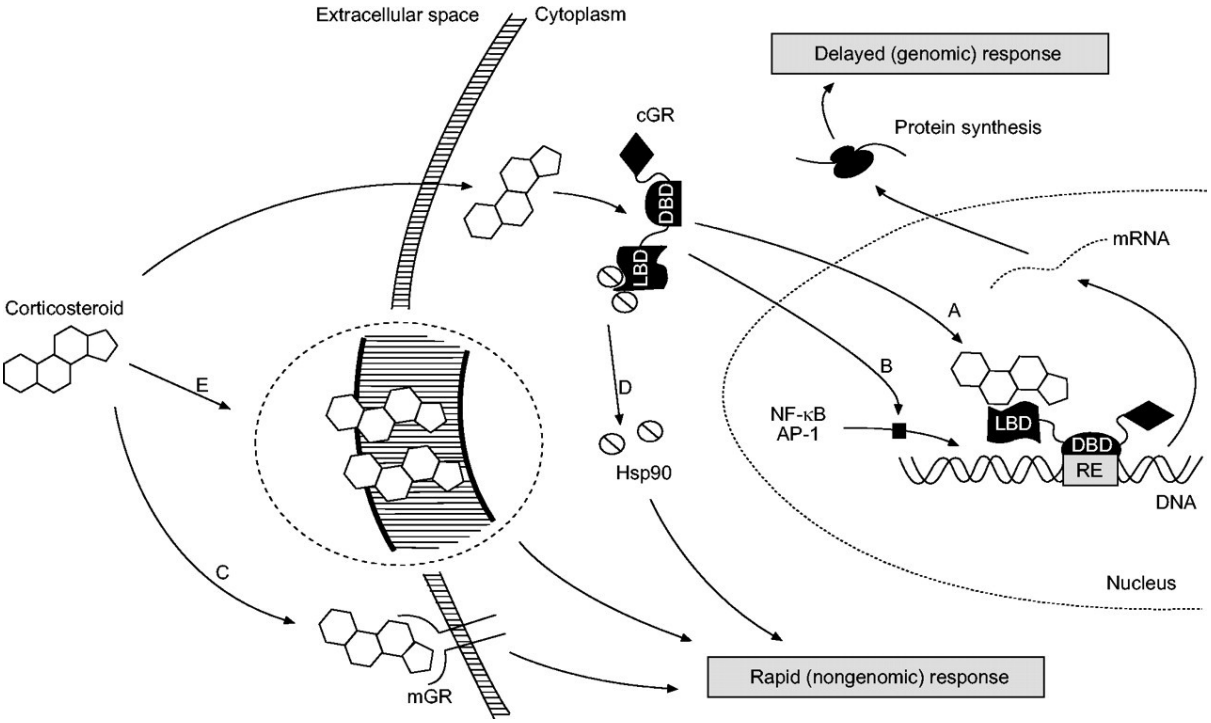


Proposed mechanism of action of the acute vasoconstrictor effect of inhaled corticosteroids in the airway. Corticosteroids facilitate the sympathetic neuromuscular signal transmission by rapidly (within 5 min) inhibiting the extraneuronal monoamine transporter (EMT) in the vascular smooth muscle cells.

Inhaled Corticosteroids would have to be administered simultaneously with bronchodilators in high and repeated or sequential doses to obtain and maintain the effect throughout the time. Since Inhaled Corticosteroids induced vasoconstriction peaks between 30 and 60 min after drug

administration, they should be administered at intervals of 30 min or less.

FIGURE 5 SCHEMATIC DIAGRAM OF THE COMPLEX CELLULAR ACTIONS OF CORTICOSTEROIDS



Genomic actions are mediated by cytoplasmic receptors, which ultimately alter transcription through A) direct DNA binding or B) transcription factor inactivation. In contrast, non-genomic actions are mediated by C) membrane-bound or D) cytoplasmic receptors, or E) nonspecific interactions with the cell membrane. cGR: cytoplasmic glucocorticoid receptor; mGR: membrane glucocorticoid receptor; LBD: ligand-binding domain; DBD: DNA-binding domain; Hsp90: heat-shock protein 90; RE: response element; NF-κB: nuclear factor-κB; AP-1: activating protein-1

TABLE 1 GENOMIC AND NON-GENOMIC ACTION OF CORTICOSTEROIDS[4]

Variables	Genomic	Non-genomic
Receptor location	Cytoplasmic	Membrane
Onset	Slow (hrs to days)	Rapid (sec to mts)

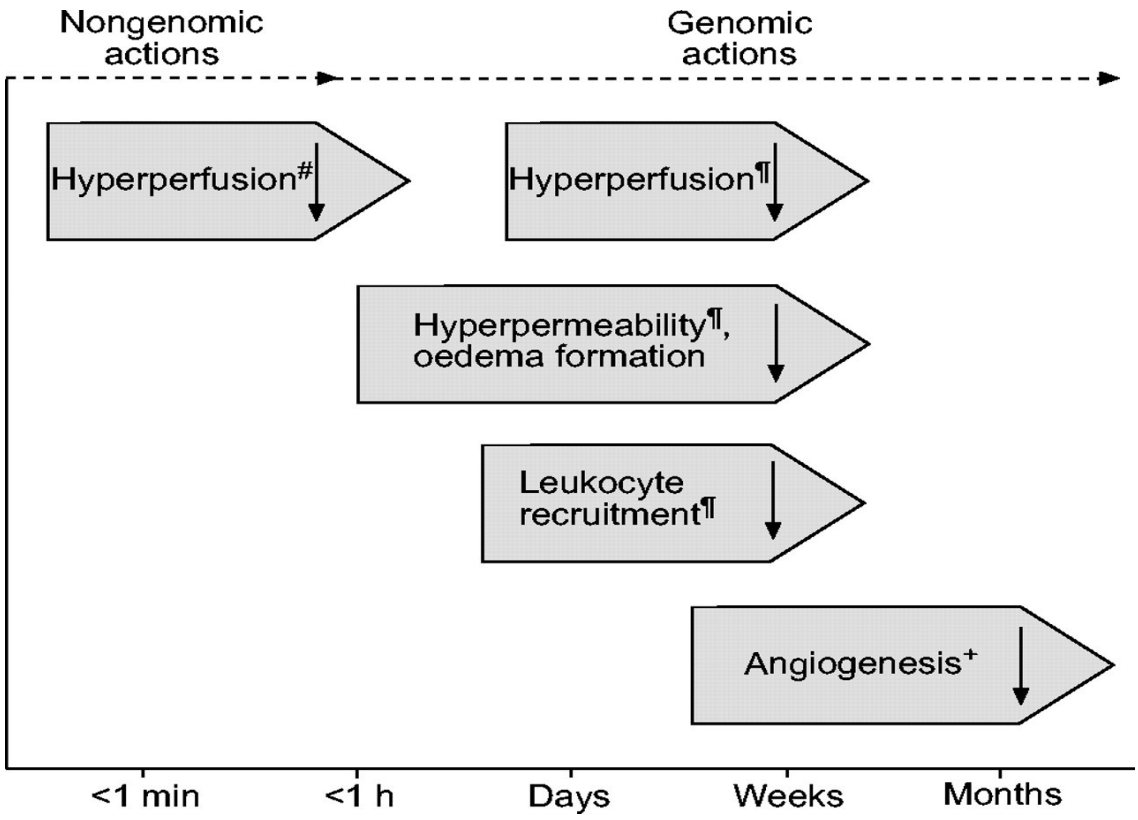
Actions	Regulation of inflammatory gene transcription	Inhibition of local catecholamine disposal
Target-effects	Angiogenesis: ↓ vessel density Hyperperfusion: ↓ Hyperpermeability: ↓ Leukocyte recruitment: inhibition	Hyperperfusion: ↓

Reduction of airway blood flow by different corticosteroids

Corticosteroids exert rapid, delayed, and long-term effects on the airway vasculature in asthma. Among these effects, corticosteroids have been shown to acutely (within minutes) alter vascular tone through non-genomic cellular actions.

Inhaled corticosteroids have been shown to acutely suppress airway hyperperfusion associated with asthma. A single dose of inhaled fluticasone propionate has been shown to decrease airway mucosal blood flow in healthy and asthmatic subjects with a maximal effect ~30 min after inhalation, and a return to baseline at 90 min. The blood flow effect increased in a dose-dependent manner up to 880 µg of fluticasone propionate, with a significantly greater effect in asthmatics than in healthy controls. The acute vasoconstrictor action has also been demonstrated after inhalation of beclomethasone dipropionate and budesonide.

FIGURE 6 Rapid (#), delayed (¶), and long-term (+) vascular effects of inhaled corticosteroids in the airway of patients with asthma. Effects are spaced vertically on the y-axis simply to facilitate reading.



In summary, the complex vascular actions of corticosteroids suggest that asthma-associated angiogenesis, hyperperfusion, hyperpermeability, and leukocyte recruitment are anti-inflammatory targets. The recently demonstrated rapid non-genomic actions of corticosteroids on airway vascular smooth muscle open new avenues for additional interventions in the pharmacotherapy of asthma.

COMPARATIVE BRONCHIAL VASOCONSTRICTIVE EFFICACY OF INHALED GLUCOCORTICOSTEROIDS[5]

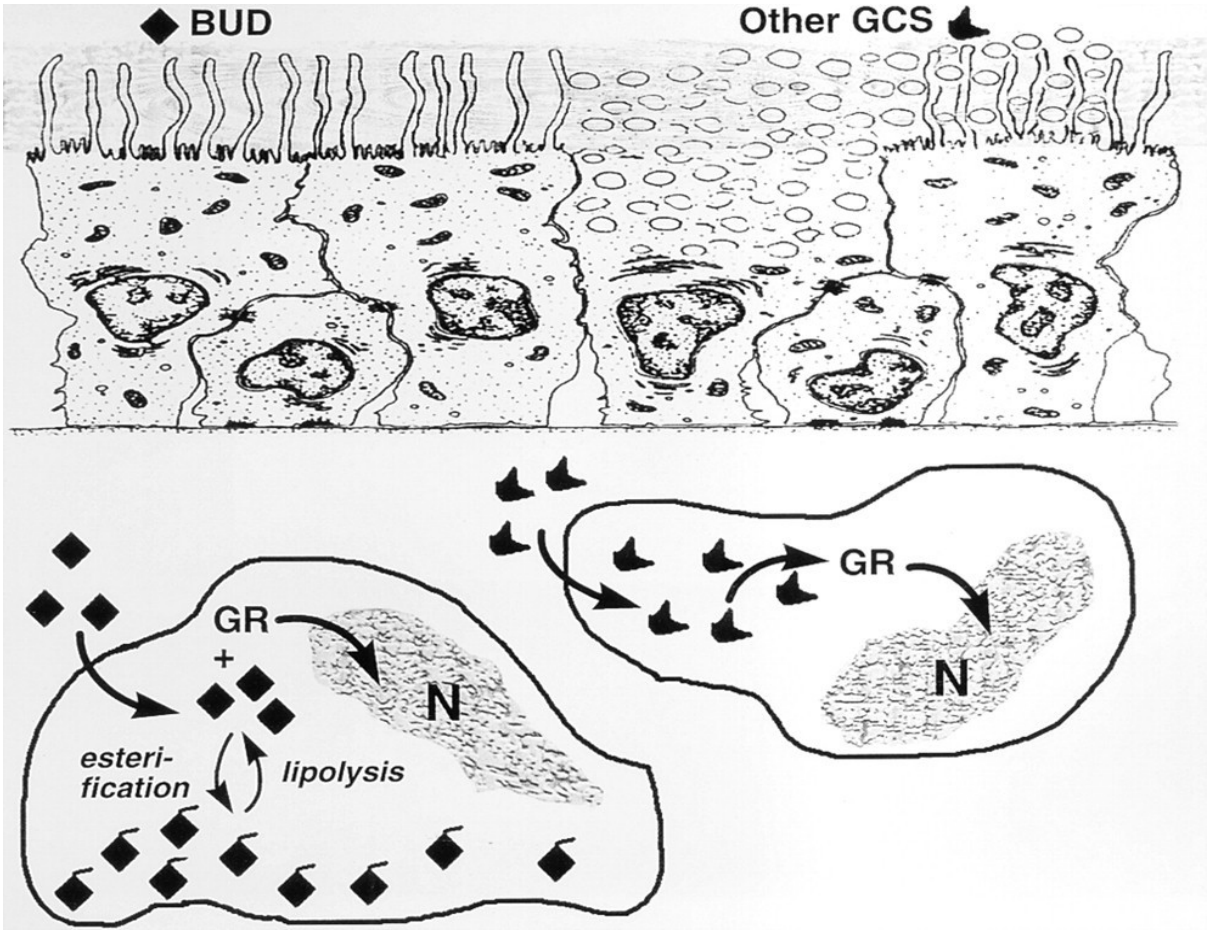
The standard screening test to determine the relative "potencies" for inhaled corticosteroids has been the McKenzie skin blanching test[21]. However, this procedure has come under criticism. The intensity of the blanching response to a glucocorticoid varies from subject-to-subject and is influenced by ambient temperature and humidity and other factors.

Using a *soluble, inert gas-uptake* method to measure airway blood flow (Qaw)[5], it was found that inhaled fluticasone propionate and budesonide caused greater vasoconstriction in the airway than beclomethasone dipropionate (see figure 9). It was also shown that for all three inhaled glucocorticosteroids, the vasoconstrictor response is greater in asthmatics than in healthy subjects

BUDESONIDE [7]

Underutilization of anti-inflammatory agents in the treatment of asthma has received widespread attention. Inhaled glucocorticosteroids are important agents for the management of asthma in children and adults. Budesonide has a high ratio of topical anti-inflammatory to systemic activity and is one of the most extensively used inhaled glucocorticoids.

FIGURE 7 LOCAL PHARMACOKINETICS OF INHALED CORTICOSTEROIDS DEPOSITED IN THE AIRWAYS[6].



First the drug has to become dissolved in the watery layer on the surface of the epithelium. Then it is absorbed into the cell where it exerts its action. Budesonide seems to be retained longer than other steroids because it forms conjugates with long-chain fatty acids within cells (410). These fatty acids—typically oleic acid—bind reversibly to the budesonide molecule; such conjugation does not appear to occur with BDP, FP, or hydrocortisone. Budesonide fatty acid conjugates appear to act as an intracellular store of inactive budesonide. Only free budesonide binds at the glucocorticoid receptor (GR), but as the airways concentration of free budesonide decreases, lipase enzymes in mucosal airway cells release more of the free compound from its conjugated fatty acids, thus raising the level of budesonide available for receptor binding.

Budesonide is a nonproteolytic, moderately lipophilic compound with rapid uptake into airway mucosa. Budesonide is a potent topical glucocorticoid with a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects when administered by inhalation in patients with asthma. Therapeutic benefits of inhaled budesonide are explained primarily by its local effects in

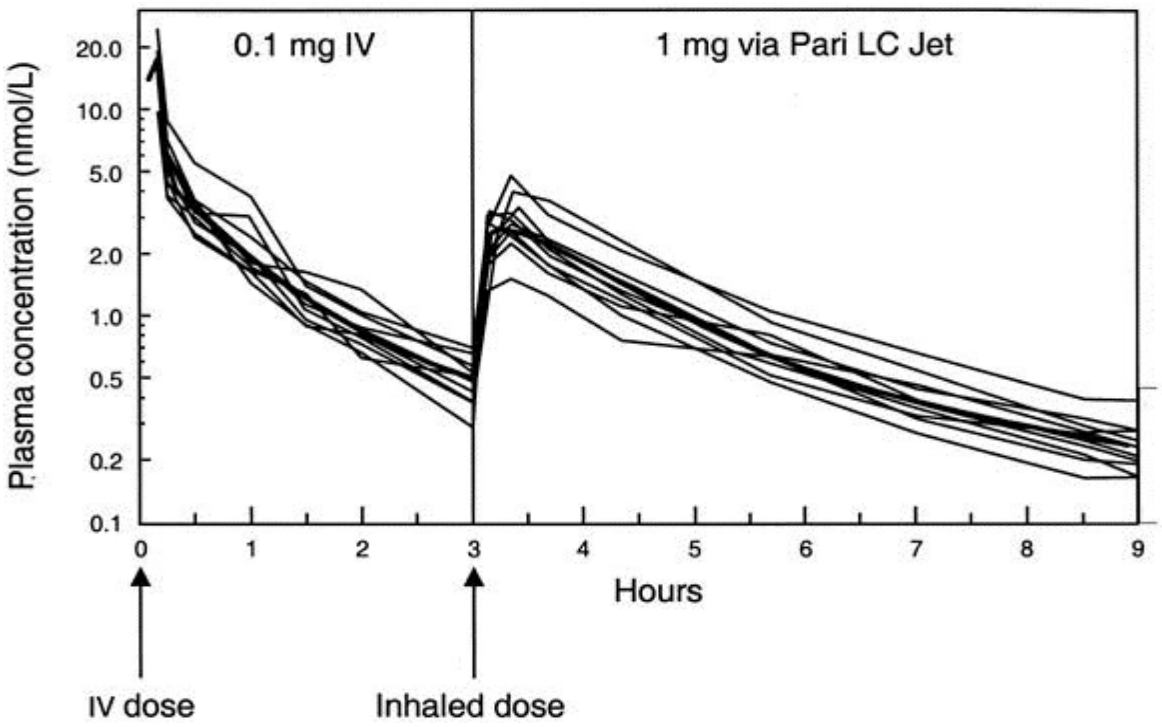
the lung. Inhaled budesonide has been shown to reduce the number of inflammatory cells and mediators present in the airways of patients with asthma. In addition, inhaled budesonide has been shown to decrease airway hyperresponsiveness after histamine, methacholine, and allergen challenges in children with asthma.

The *pharmacokinetics* of BIS (Budesonide inhalation suspension) administered by nebulisation has been well characterized in children. Only jet nebulizers are recommended for administration of BIS. Absorption of nebulised budesonide from the lungs is rapid, with peak plasma concentrations reached approximately 10 to 30 minutes after the start of nebulisation (see figure 8). The budesonide deposited in the oropharynx is assumed to be swallowed and eventually absorbed from the gastrointestinal tract; however, because of extensive first-pass elimination of oral budesonide (approximately 85%-90%), very little drug is systemically absorbed. In 3- to 6-year-old children with asthma, the total systemic availability (pulmonary plus oral) of BIS (Budesonide inhalation suspension) by a jet nebulizer was approximately 6% of the labeled dose.

In children 3 to 6 years of age, nebulisation of BIS 1 mg, using jet nebulizer-compressor systems that deliver between 5% and 17.8% of the labelled budesonide dose in vitro are expected to deliver a clinically effective dose.

Overall, the pharmacokinetic profile of BIS (Budesonide inhalation suspension) allows for a long duration of local therapeutic effects (see figure 7) with minimal systemic exposure. This novel formulation of budesonide is a long-awaited therapeutic option for the treatment of persistent asthma in infants and children.

FIGURE 8 BIS (Budesonide inhalation suspension) plasma concentration-time data in children 3 to 6 years of age (n = 10)[9]



REVIEW OF LITERATURE

Gustavo J. Rodrigo, MD, Emergency Department, Hospital Central de las, Montevideo, Uruguay conducted a meta analysis of the best evidence available on the early (1 to 4 h) clinical impact of Inhaled Corticosteroids for patients with acute asthma in the emergency department (ED) setting. He reviewed seventeen randomised controlled trials (470 adults and 663 children and adolescents) conducted between the period of 1966 to 2006. His review suggested that Inhaled Corticosteroids present early beneficial effects (1 to 2 h) when they were used in multiple doses administered in time intervals ≤ 30 min over 90 to 120 min. The non-genomic effect is a possible candidate by covering the link between molecular pathways and the clinical effects of corticosteroids[4].

Van Essen-Zandvliet et al.' showed an improvement in FEV, within 5 hours after inhaled

budesonide was given to children aged 7 to 13 years with mild stable asthma.

Schuh et al, Division of Paediatric Emergency Medicine, Hospital for Sick Children, Ontario, Canada conducted a randomised, double-blind controlled trial called *"High-Dose Inhaled Fluticasone Does Not Replace Oral Prednisolone in Children With Mild to Moderate Acute Asthma"*. They determined whether there is a significant difference in the percentage of predicted forced expiratory volume in 1 second in children with mild to moderate acute asthma treated with either inhaled fluticasone or oral prednisolone. The study was conducted between 2001 and 2004 involving 69 previously healthy children 5 to 17 years of age with acute asthma and forced expiratory volume in 1 second at 50% to 79% predicted value. The study concluded that airway obstruction in children with mild to moderate acute asthma in the emergency department improves faster on oral prednisolone than inhaled fluticasone[10].

Rowe BH et al, Department of Emergency Medicine, University of Alberta, Edmonton, Canada et al conducted a review of Randomised controlled trials to evaluate the benefits of *"Early emergency department treatment of acute asthma with systemic corticosteroids"*. The study found that use of corticosteroids within 1 hour of presentation to an ED significantly reduces the need for hospital admission in patients with acute asthma. Benefits appear greatest in patients with more severe asthma, and those not currently receiving steroids. Children appear to respond well to oral steroids[11].

A Randomised Controlled Trial of "*Inhaled Flunisolide in the Management of Acute Asthma in Children"* conducted by Albert K. Nakanishi, From the Department of Pediatrics (Dr. Nakanishi), St. Louis University School of Medicine, St. Louis, found that inhaled corticosteroids are useful in the management of acute asthma in children; however, spirometry data suggested a more rapid resolution of asthma with Oral Corticosteroids[12].

EE Matthews, MD Princess Royal Hospital, Apley Castle, Telford, UK in a prospective, double-blind, randomised controlled study of *"Nebulised budesonide versus oral steroid in severe exacerbations of childhood asthma*" compared nebulised budesonide (2 mg 8 hourly) with oral prednisolone (2 mg/kg at entry and again at 24 h) in 46 children admitted to hospital with severe asthma exacerbations. Efficacy variables (including lung function measurements such as the primary outcome variable, Forced Expiratory Volume in 1 second (FEV1) and symptoms) were measured 24 h after treatment initiation. The data show nebulised budesonide to be at least as effective as oral steroid in improving lung function and symptom severity in severe exacerbations of childhood asthma[13].

Lillian Sung, MD, et al conducted a "*Randomised, Controlled Trial of Inhaled Budesonide as an Adjunct to Oral Prednisone in Acute Asthma ".* They compared the clinical effect of nebulised budesonide with placebo in acute pediatric asthma at the Children's Hospital of Eastern Ontario, University of Ottawa, Canada. They found no significant differences in the primary outcome measure (PIS - Pulmonary Index Score) between the 2 groups. However, the PIS at 1 hour had a tendency to be lower in the budesonide group (median = 5) as compared with the placebo group (median = 6; p = 0.07). Survival analysis of release/discharge from the ED showed a more rapid rate in the budesonide group as compared with the placebo group (p = 0.02). No adverse effects were seen[14].

Edmonds et al conducted a systematic review of the literature with meta-analysis to determine the benefit of inhaled Corticosteroids for the treatment of patients with acute asthma managed in the emergency department. On the basis of six randomised controlled trials (six adult, two pediatric), the authors found that patients treated with inhaled Corticosteroids were less likely to be admitted to the hospital (odds ratio, 0.33; 95% confidence interval, 0.17 to 0.64); additionally, they demonstrated a significant improvement in FEV1 at 2 h of treatment[15].

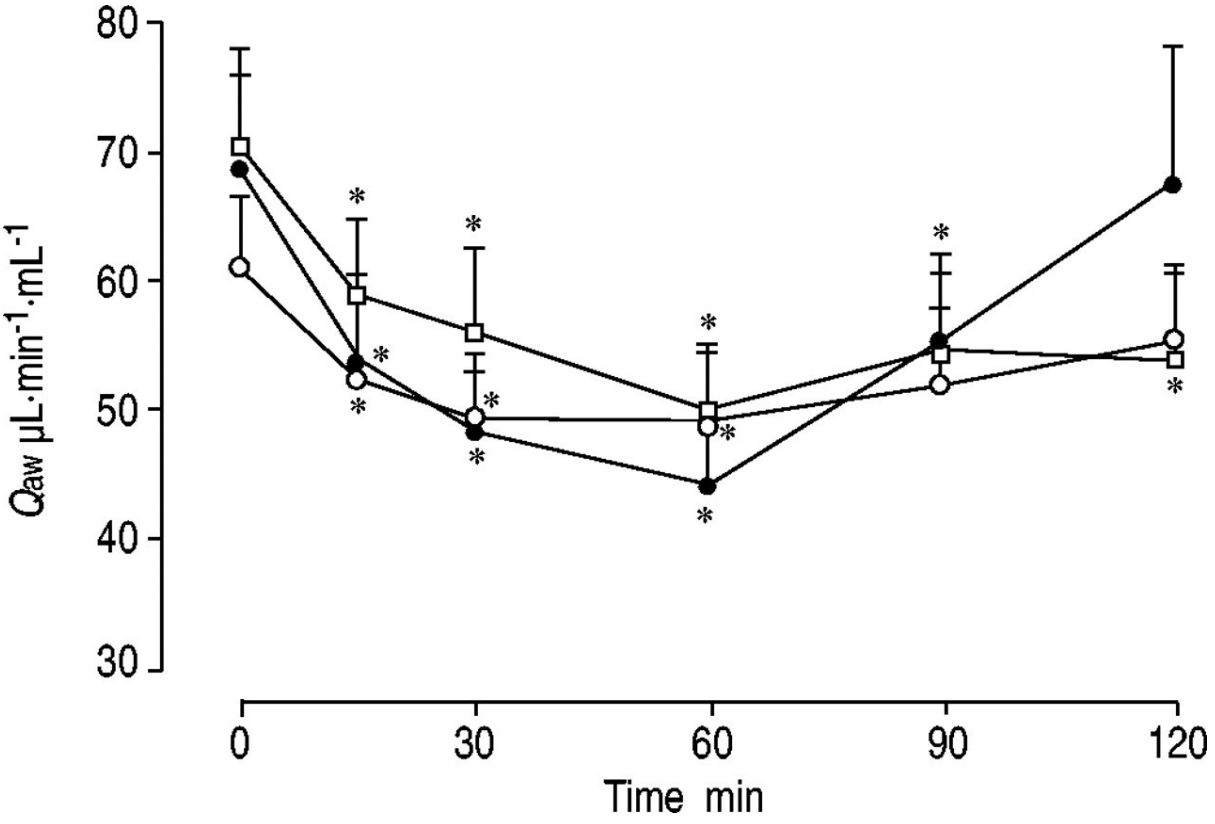
In a Randomised double-blind, double-dummy and placebo-controlled clinical trial evaluating the efficacy of *"Nebulised budesonide to treat acute asthma in children"* Geórgia K. M. Milani found that a combination of single-dose nebulised budesonide and salbutamol may be as effective as oral prednisone to improve symptom severity, but the latter increases haemoglobin saturation in exacerbation of asthma[16].

Devidayal, Singhi S, et al from the Department of Pediatrics, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India evaluated the "*Efficacy of nebulised budesonide compared to oral prednisolone in acute bronchial asthma*". The baseline characteristics of the two groups were similar, but after three doses of nebulisation oxygen saturation, respiratory rate, pulmonary index and respiratory distress score were significantly improved in the budesonide group compared to prednisolone group ($p < 0.01$). The proportion of patients who were fit for discharge at the end of 2 h after the third dose of nebulisation was significantly higher in the budesonide group than in the prednisolone group (22/ 41, 54% vs 7/39, 18%, $p < 0.001$). The data suggest that a combination of nebulised salbutamol and budesonide should be preferred in the emergency room management of children with acute moderate to severe exacerbation of asthma and who are not on prior oral or inhaled steroid therapy[17].

In a study done by E.S.Mendes et al, Pulmonary and Critical Care Division, Dept of Medicine, University of Miami, FL, USA a *soluble, inert gas-uptake* method was used to measure airway blood flow (Qaw)[6]. Mendes, E.S., Pereira et al (2003) did a study on *"Comparative bronchial vasoconstrictive efficacy of inhaled glucocorticosteroids"*. In summary, this investigation showed that inhaled fluticasone propionate and budesonide cause greater vasoconstriction in the airway than beclomethasone dipropionate (see figure 9). It was also shown that for all three inhaled

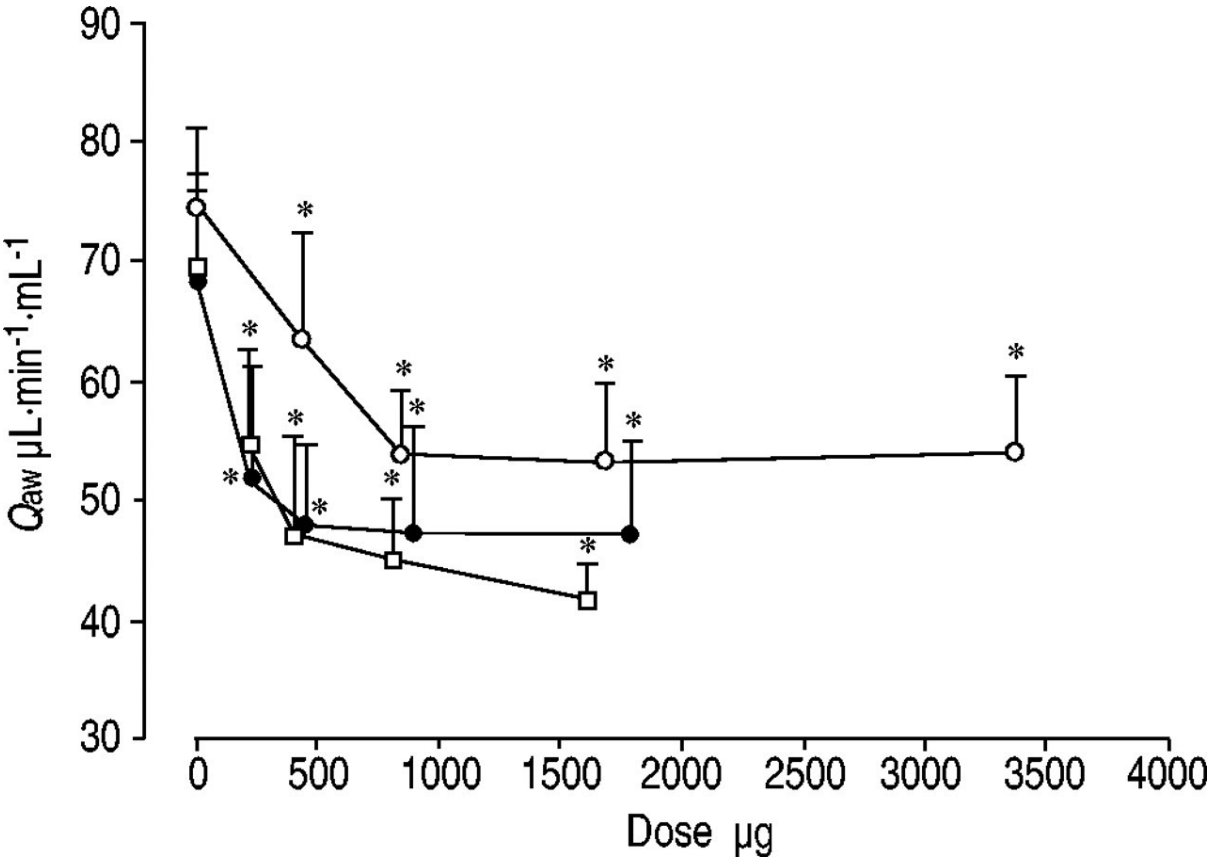
glucocorticosteroids, the vasoconstrictor response is greater in asthmatics than in healthy subjects[5].

FIGURE 9— Airway blood flow (Qaw) before and after the inhalation of fluticasone (•), beclomethasone (○) and budesonide (□) in asthmatic subjects (n=10). Data are presented as mean±sd. *: p<0.05 versus baseline value[5]



These findings indicate drug-specific and disease-specific in vivo potency differences in both bioavailability and vasoconstrictive efficacy among three commonly prescribed glucocorticoid metered-dose inhalers. The relative vasoconstrictive efficacies of Beclomethasone, Fluticasone and Budesonide were 1, 1.9 and 2.7, respectively, in asthmatic subjects and 1, 3.3 and 3.0, respectively, in healthy subjects.

FIGURE 10 Dose/response relationship between inhaled fluticasone(•), beclomethasone (○) and budesonide (□) dose and airway blood flow (Qaw) in asthmatics (n=10). Data are presented as mean±sd. : p<0.05 versus baseline value[5]



De Blic J, et al evaluated the *"Efficacy of nebulised budesonide in treatment of severe infantile asthma"* in a double-blind, placebo-controlled study, where 40 infants with severe asthma received either nebulised budesonide (1 mg) or placebo twice daily for 12 weeks, followed by a follow up period of up to 12 weeks.. Significantly fewer patients in the budesonide group had exacerbations requiring administration of oral corticosteroids, and for those who had such exacerbations, the duration of oral corticosteroid therapy decreased. The incidence of daytime and night time wheezing was lower in the budesonide group than in the placebo group. He therefore concluded that nebulised budesonide (1 mg twice daily) is a well-tolerated and efficient treatment for severe infantile asthma (J_Allergy Clin

Immunol 1996; 98.'14-20.) [18].

Volovitz B, et al From the Asthma Clinic, Department of Pediatrics , Schneider Children's Medical Center of Israel, Tel Aviv University (1998) did a controlled comparative study on *"Effectiveness and safety of inhaled corticosteroids in controlling acute asthma attacks in children who were treated in the emergency department compared with oral prednisolone"*. In conclusion, this study shows that in children with moderately severe asthma attacks who were treated in the ED, a short-term dose schedule of inhaled budesonide given by means of turbohaler, starting with a high dose and followed by a rapid decrease in dose over 8 days, is at least as effective as oral prednisolone treatment without the suppression of serum cortisol levels[19].

Manjra, et al Paediatric Allergy and Asthma Centre, Westville Hospital, Westville, South Africa (2000) designed a multi-centre, randomised, double-blind, study to compare the Efficacy of nebulised fluticasone propionate with oral prednisolone in children with an acute exacerbation of asthma. The study demonstrated that nebulised fluticasone propionate is at least as effective as oral prednisolone in the treatment of children presenting with an acute exacerbation of asthma[20].

JUSTIFICATION OF THE STUDY

- Corticosteroids have been have been used in the management of acute exacerbation of asthma[25, 27, 28].

- Intravenous[29] and oral administration[25] of corticosteroids have been used with good results, aside from some controversial findings for the intravenous route.

- Oral administration was found to be equally effective to the intravenous route in the initial treatment of acute asthma.

- Data from some studies have suggested that intravenous and oral corticosteroids produce no immediate beneficial effects in the management of acute exacerbation of asthma[30, 31].

- Inhaled corticosteroids have greater anti-inflammatory and antiasthma potency and fewer systemic effects than oral corticosteroids and they are delivered directly into the lung.

- Furthermore recent research has revealed that inhaled corticosteroids produce rapid beneficial effects (through non –genomic action) by causing vasoconstrictive effects on the bronchial vasculature thereby relieving congestion in airways and potentiating the bronchodilator effects of inhaled β_2 agonists[5].

- Therefore Inhaled Corticosteroids are excellent candidate agents for controlling acute asthma.

- Various inhaled corticosteroids have been used in acute asthma in numerous studies. Among these agents *budesonide* has shown to be more effective because of its favourable local pharmacokinetics and potent bronchial vasoconstrictive properties[5, 6, 7].

- Some recent studies have investigated the effect of inhaled corticosteroids in the exacerbation of asthma, but their role in acute asthma and the preferred dose schedule for controlling acute attacks in children have not been established.

- In a meta-analysis preformed by Rodrigo and Rodrigo[4], involving seventeen randomised

controlled trials, it has been shown that high doses of inhaled corticosteroids had rapid beneficial effects in improving pulmonary function thereby increasing early discharges.

- This is a very relevant finding since hospital admissions count for the largest part of direct health costs for asthma.

- Hence the present study is aimed at evaluating immediate beneficial effects of inhaled corticosteroids (budesonide) in the management of acute exacerbation of asthma in children (4 – 12 yrs) in an Emergency Department setting.

AIM OF THE STUDY

To determine the early clinical benefit of Inhaled Corticosteroids (Nebulised Budesonide) for the treatment of children (4 – 12 yrs) with *Acute Severe Asthma* managed in the emergency department (ED) compared to Systemic Corticosteroids (oral prednisolone).

METHODS

The Study was designed as a *Randomised double blind, placebo controlled trial* and it was conducted at the *Emergency Department* of the Institute of Child Health & Hospital for Children, Chennai between the period of May 2007 to November 2008.

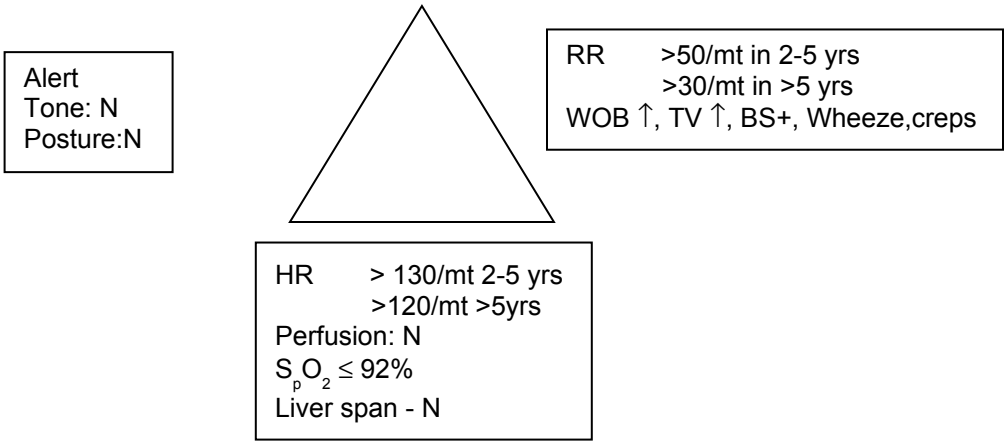
Setting and population

Known asthmatic children aged between 4 to 12 years of both sexes presenting with cough, cold and acute onset of breathlessness were initially screened after stabilising the child. Life-threatening presentations were excluded from the study.

INCLUSION CRITERIA

- Children over 4 years of age presenting with acute exacerbation of asthma to the Emergency Department of the Institute of Child Health.
- Known case of asthma

  Case definition for Acute Severe Asthma[22].



EXCLUSION CRITERIA

Children with

- congenital heart disease
- chronic lung disease
- X-ray and/ clinical evidence of pneumonia
- Higher severities of asthma e.g. life threatening Asthma

Subsequently the remaining children were subjected to X-ray. Those children having clinical/ X-ray evidence of pneumonia or cardiomegaly or other lung pathologies are excluded from the study. The remaining children were assessed for the severity of Asthma. Those children coming under the category of Acute Severe Asthma (see triangle above) were included in the study after obtaining parental consent and informing the child. Children of those parents who didn't give parental consent were excluded from the study.

Randomisation

Opaque sealed envelopes containing labels A or B were developed and kept in the Emergency Department in a single box.

As soon as the child was recruited into the study one sealed envelope was opened and the child managed as per the group assigned in the envelope.

The *study group or budesonide group* received three doses of nebulised salbutamol (0.15 mg/kg) and budesonide respirator solution (800 µg) at intervals of 20 minutes and a single dose of placebo tablets. Similarly *the control group or prednisolone group* received three doses of nebulised salbutamol (0.15 mg/kg) along with placebo solution at intervals of 20 minutes and a single dose of oral prednisolone (2 mg/kg) (see figure 11). The study and control groups were assessed every 20 minutes for upto 1 hour. The parameters that were assessed include heart rate, respiratory rate, oxygen saturation, PEFR (Peak Expiratory Flow Rate) at the end of one hour and at 4 hrs and fitness for discharge at the end of 2 hours.

Blinding

In this trial, children were assigned treatments at random and neither the subject nor the person delivering the drug and measuring the outcome know whether the subject received an active drug or a placebo. Hence it is double-blinded.

The *study group or budesonide group* received three doses of nebulised salbutamol (0.15 mg/kg) and 3.2 ml of budesonide respirator solution (800 µg) at intervals of 20 minutes whereas the

control or prednisolone group received three doses of nebulised salbutamol (0.15 mg/kg) along with 3.2 ml of placebo respirator solution at intervals of 20 minutes. The placebo respirator solution and budesonide respirator solution were stored in dark brown containers that looked similar and labelled as either A or B. For example, if the placebo respirator solution is labelled as A then the budesonide solution would be labelled as B and vice versa. So each patient received 3.2 ml of either the placebo solution or budesonide solution. This ensured that the study group patients received the appropriate dose of budesonide i.e. 800µg as each ml of budesonide solution contains 250µg (hence 3.2 ml contains 800µg).

In the same manner the study group received placebo tablets (powdered) whereas the control group received prednisolone tablets (powdered) which had similar appearances. To avoid bias in administering the tablets, the prednisolone (5mg) tablets were powdered and stored in small plastic packets which were sealed tightly so that each packet contained 5 mg of prednisolone. Six such packets each containing 5 mg of prednisolone were then put into a big envelope and sealed. Thirty such envelopes, each containing six packets of powdered prednisolone were prepared and kept in the emergency department. Similarly, placebo powder which had the same appearance as that of the prednisolone powder was packed similarly into small plastic packets six of which were then put into a big envelope. Thirty such envelopes, each containing six packets of placebo powder were prepared and kept in the emergency department. The prednisolone and the placebo envelopes containing six prednisolone or six placebo packets each respectively were then labelled as either A or B. For example, if the prednisolone envelopes were labelled as A then the placebo envelopes were labelled as B and vice versa.

The powdered prednisolone tablets or placebo tablets were administered orally after initial stabilisation and before starting nebulisation. Thus children recruited into group A received 4 (4 – 6yrs)

or 6 (6-12 yrs) packets from envelope A according to the age of the patient. Similarly children recruited into group B received 4 (4 – 6yrs) or 6 (6-12 yrs) packets from envelope B. This ensured that the children in control group received the appropriate dose of prednisolone (20 mg for 4-6 yrs, 30 mg for 6-12 yrs).

Thus *budesonide solution is paired with placebo tablets (powder)* whereas *prednisolone is paired with placebo respirator solution*. For example if the budesonide solution was labelled as A, then the placebo tablets were labelled as A, whereas the prednisolone tablets and placebo solution were labelled as B. So children assigned A would have got budesonide solution and placebo powder, whereas children assigned B would have got prednisolone tablets and placebo solution. It is ensured that all patients in each group received both the nebuliser solution and tablets (powdered). In case any child deteriorated during the trial, the trial was discontinued and the child was managed as per the regular ER protocol for higher severities of asthma.

OUTCOME MEASURES

(All measured from 0-4 h of the protocol)

Primary outcome

1. Fitness for discharge at the end of 2 hrs, based upon clinical severity scoring system[16] (a score of ≤ 0.4 is taken as fit for discharge, see table 2).

Secondary outcomes

1. Heart rate
2. Respiratory rate

3. Oxygen saturation
4. Peak expiratory flow rates (PEFR) (at 1 hr, 4 hrs)
5. Adverse effects

Table 2 -Clinical Scoring System[26]

Variable	Score=0	Score=1
Heart rate	<120/min for > 5 yrs <130/min for 2-5 yrs	>120/min for > 5 yrs >130/min for 2-5 yrs
Respiratory rate	<50/min 2 – 5 yrs <30/min for >5 yrs	>50/min 2-5 yrs > 30/min for >5 yrs
Dyspnea	Absent or mild	Moderate or severe
Accessory muscle use	Absent or minimal	Moderate or severe
Wheezing	Absent or end expiratory only	Throughout expiration or expiratory

Note: the score was expressed by adding the number of positive values (i.e. score =1) for an individual patient, as a fraction of the total number of variables i.e. 5. The final score ranged from 0 to 1.0, increasing with severity.

SAMPLE SIZE

The primary outcome measure (fitness for discharge) was used to calculate the sample size. Assuming expected difference in improvement in discharge rates between Inhaled Corticosteroids and Systemic Corticosteroids to be 20%. Sample size was calculated with power of 80%, α error of 20% and β error of 5%.

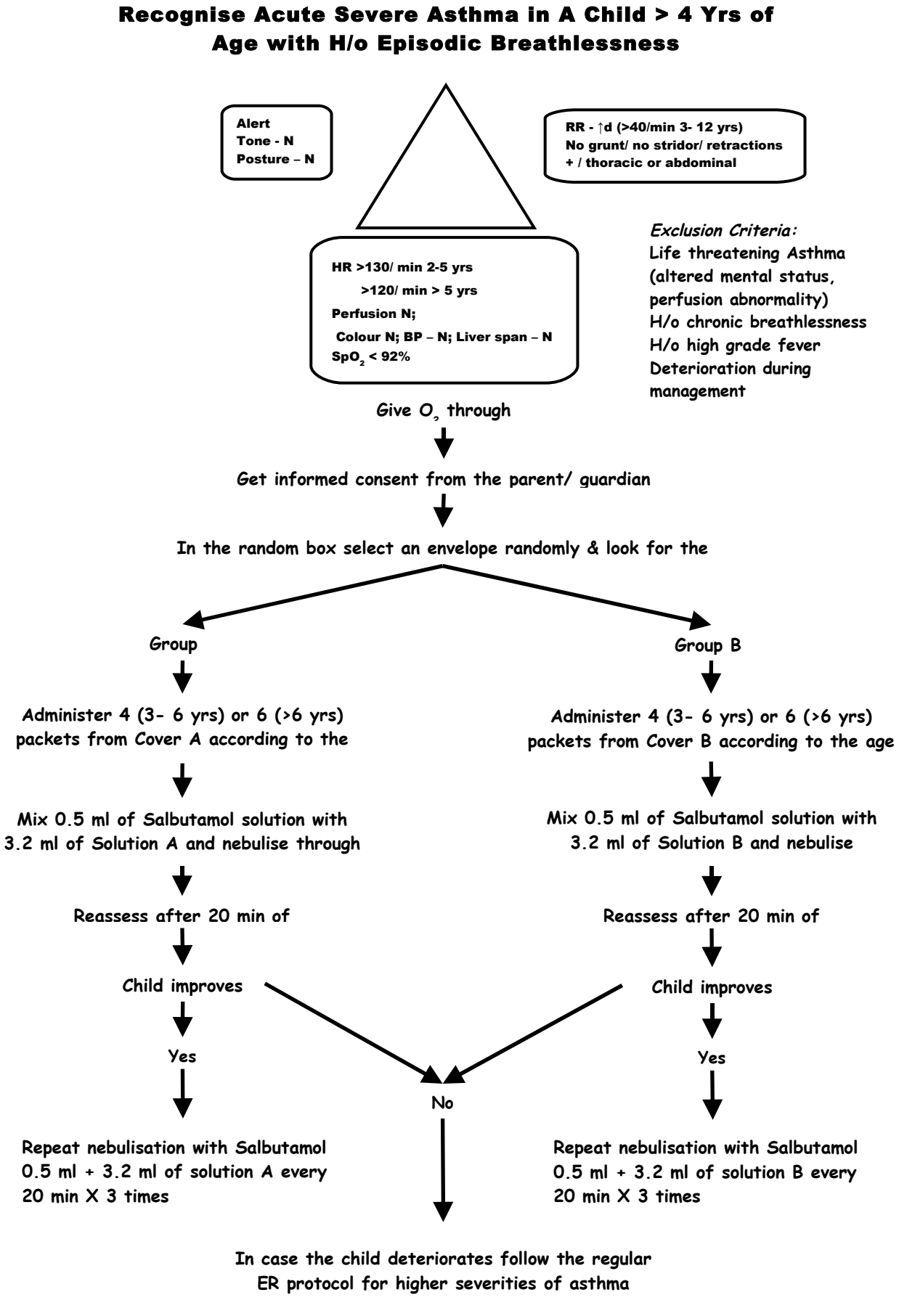
ALPHA ERROR	20%
BETA ERROR	5%

POWER	80%
SAMPLE SIZE	60

STATISTICAL ANALYSIS

Statistical analysis for the outcomes were done by using Chi square test for *fitness for discharge*, paired t-test for *parametric variables* in each group and two-sample (unpaired) t-test for estimating difference in the improvement in parametric variables between the groups. A *p* value of less than 0.05 is considered as significant.

FIGURE 11 PROTOCOL FOR MANAGEMENT OF CHILDREN WITH ACUTE SEVERE ASTHMA RECRUITED INTO THE STUDY



RESULTS

Eighty five asthmatic children aged between 4 – 12 years presenting to the emergency department with cough, cold and acute onset breathlessness were initially screened. Fifteen children with features of life-threatening asthma were excluded from the study. The rest of the children were subjected to an X-ray. Out of these, five children had X-ray evidence of bronchopneumonia who were then excluded from the study. Parents of four children declined consent. The remaining sixty one (61) children were recruited in to the study after obtaining consent.

Thirty one (31) children were randomised into prednisolone group and thirty (30) children into budesonide group and treated accordingly (see figure 12). The baseline characteristics of both the groups were comparable as shown in table 5. These children were assessed at regular intervals of 20 minutes for upto one hour for parameters like heart rate, respiratory rate and oxygen saturation. Peak Expiratory Flow Rates were done at the end of 1 hr and at 4 hrs. Only seventeen children in prednisolone group and eighteen children in budesonide group were able to perform FVC (Forced Vital Capacity) manoeuvre. Hence PEFRs were measured only in these children at the end of one hour and again at 4 hrs after starting treatment. The fitness for discharge was assessed at the end of 2 hrs using the clinical severity scoring system shown in table 2. Children with a score of 0.4 or less were taken as fit for discharge.

FIGURE 12 TRIAL PROFILE OF CHILDREN PRESENTING TO THE EMERGENCY DEPARTMENT WITH ACUTE SEVERE ASTHMA

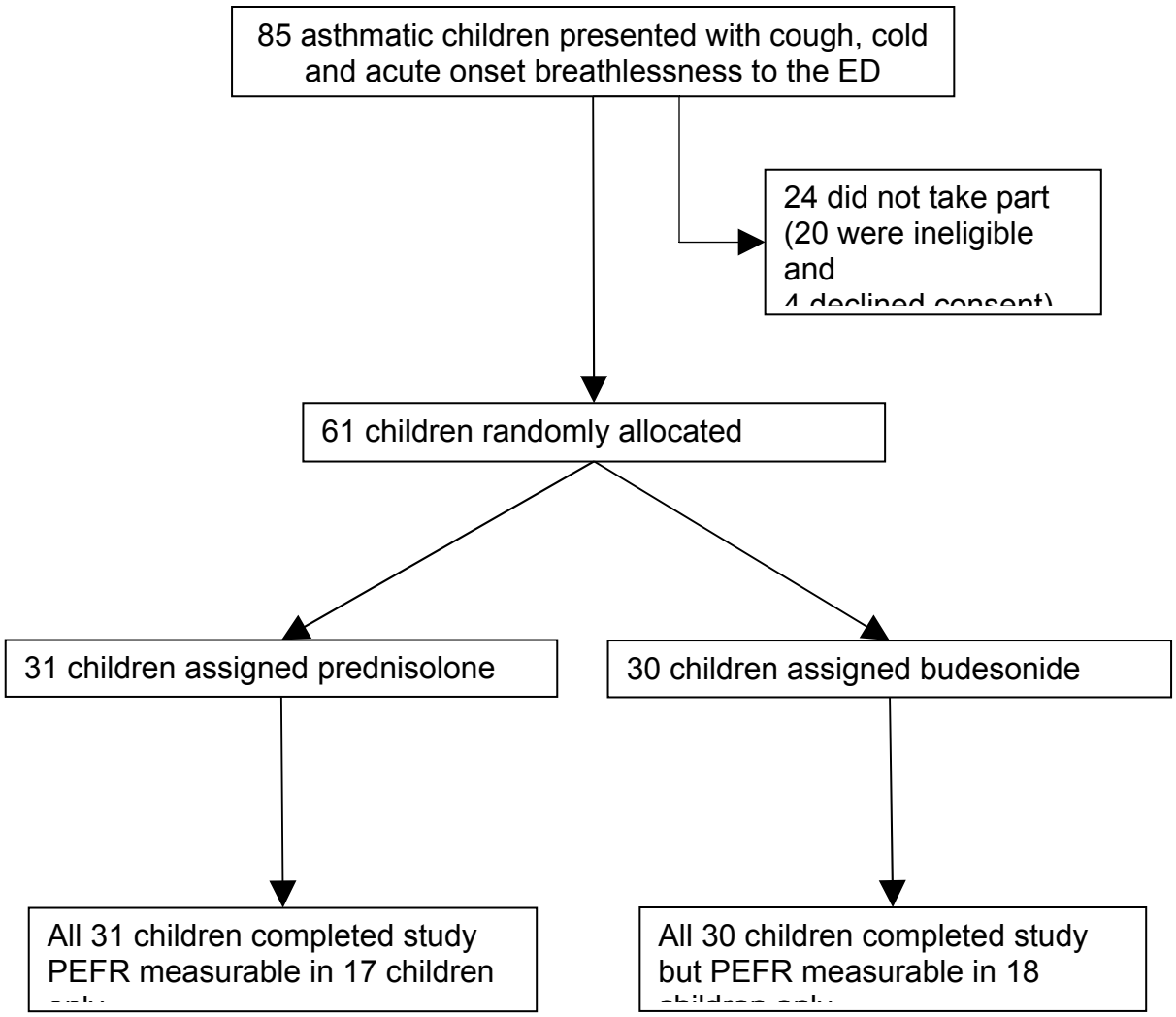
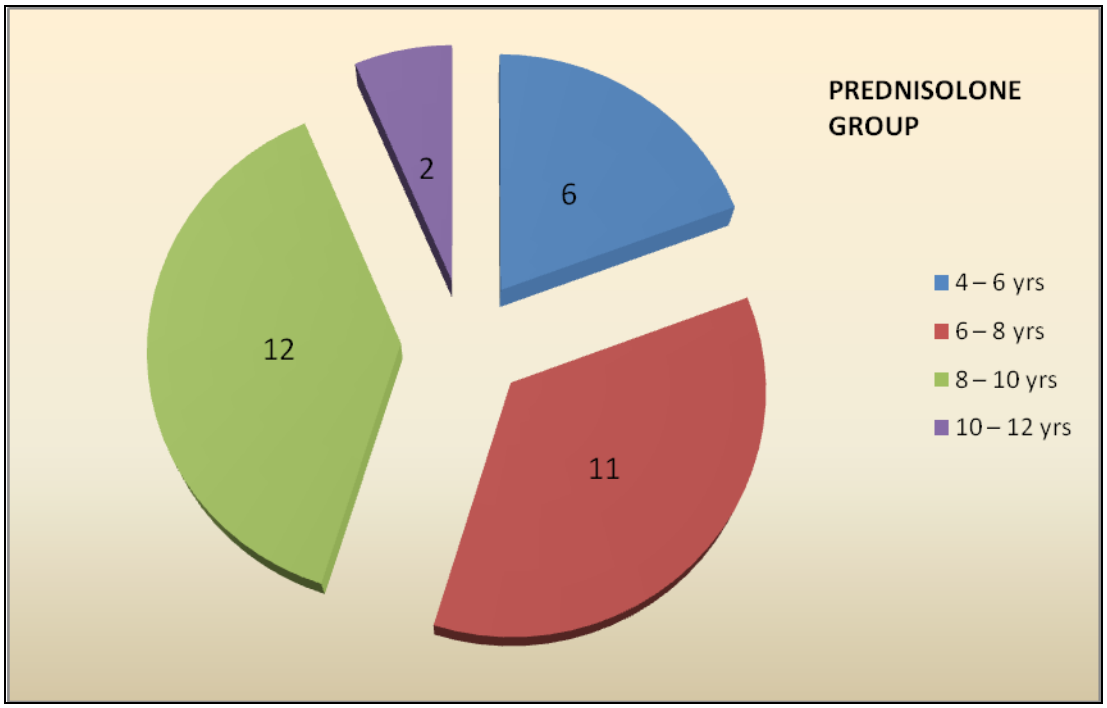

85 asthmatic children presented with cough, cold and acute onset breathlessness to the ED
24 did not take part (20 were ineligible and
61 children randomly allocated
31 children assigned prednisolone
30 children assigned budesonide
All 31 children completed study PEFR measurable in 17 children
All 30 children completed study but PEFR measurable in 18

Table 3 Demographic characteristics of patients on arrival at the Emergency Department

Age Groups	Prednisolone group			Budesonide group		
	Boys	Girls	Total	Boys	Girls	Total
4 – 6 yrs	4	2	6	2	2	4
6 – 8 yrs	6	5	11	6	5	11
8 – 10 yrs	4	8	12	6	4	10
10 – 12 yrs	1	1	2	2	3	5
Total	15	16	31	16	14	30

Of the thirty one children recruited into prednisolone group fifteen were boys and sixteen were girls. Of the thirty children recruited into budesonide group sixteen were boys and fourteen were girls. There were six children between 4-6 yrs in prednisolone group and four children in the same age group in budesonide group. Similarly the numbers of children in other age groups were comparable between the two groups as shown in table 3.

DEMOGRAPHIC STATISTICS OF PREDNISOLONE GROUP



DEMOGRAPHIC STATISTICS OF BUDESONIDE GROUP

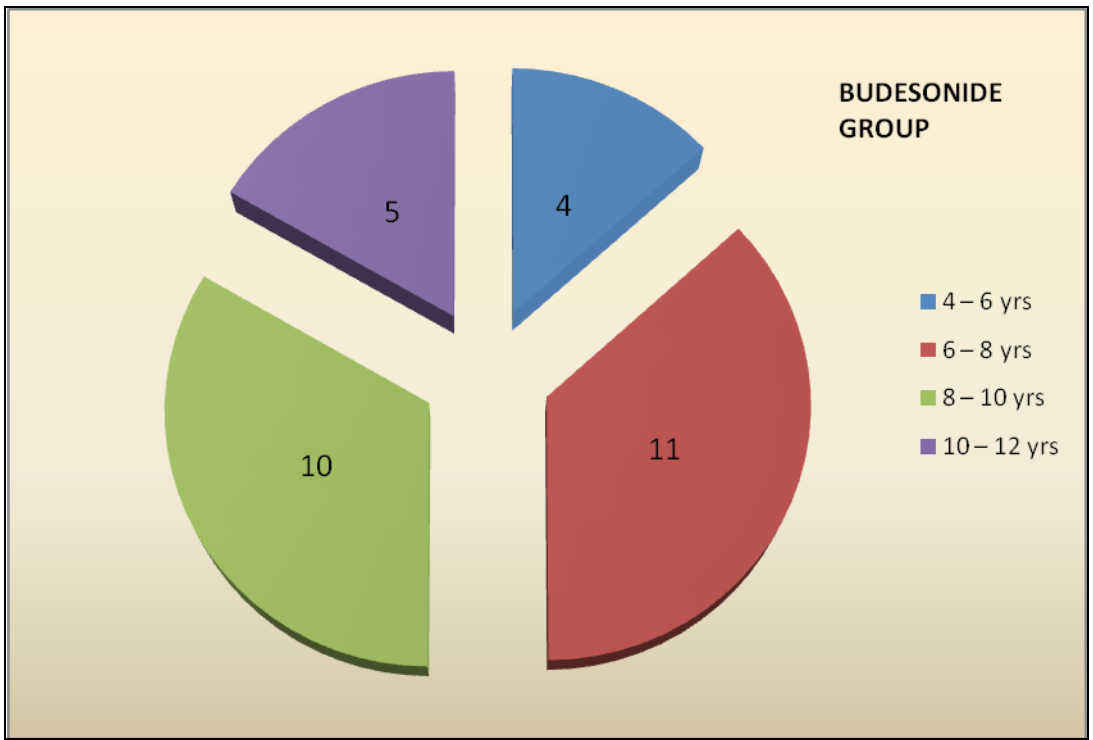


Table 4 Nutritional status

Weight for age %	Prednisolone group (n=31)	Budesonide group (n=30)
Normal (> 80 %)	23	18
Grade I PEM (71 – 80)	8	10
Grade II PEM (< 70 %)	1	2

Nutritional status of children participating in the study was assessed using the weight for age. According to Indian Academy of Pediatrics classification, one child in prednisolone group and two children in budesonide group had grade II PEM. Similarly, eight children in prednisolone group and ten children in budesonide group had grade I PEM. The remaining children in both the groups were of the normal weight for age. Thus both the prednisolone group and the budesonide group were comparable with respect to the nutritional status.

Table 5 Baseline comparison

Variable	Prednisolone group n = 31	Budesonide group n = 30	*p* value
Age	7.14 ± 1.93	7.8 ± 1.93	0.19
Sex (M : F)	15:16	17:13	
Nutritional status (W/A)	83.74 ± 6.35	83.13 ± 8.82	0.76
Respiratory rate	53.81 ± 8.86	50.67 ± 6.02	0.112
Heart rate	148.19 ± 11.86	143.53 ± 11.66	0.127

O2 saturation	93.39 ±1.022	98.37 ± 1.098	0.940
PEFR (at 1 hr) (L/min)	185.88 ± 40.05 (n = 17)	180.56 ± 38.15 (n = 18)	0.69
Clinical Severity Scoring	0.677 ± 0.17	0.66 ± 0.18	0.69

As seen from the above table, children in both the groups were matched for categorical variables like age, sex and nutritional status (weight for age). Similarly both the groups were matched for continuous variables like initial heart rate, initial respiratory rate, initial oxygen saturation, PEFR at one hrs and clinical severity scoring at presentation with *p* values insignificant i.e. >0.05.

Comparison in the outcome measures

Heart rate

Children in both groups showed a progressive decrease in heart rate with treatment. The average initial heart rate for prednisolone group was 148.2 ± 11.86 which showed a significant decrease to an average heart rate of 123.42 ± 12.64 at 60 min ($p < 0.001$) (see table 6).

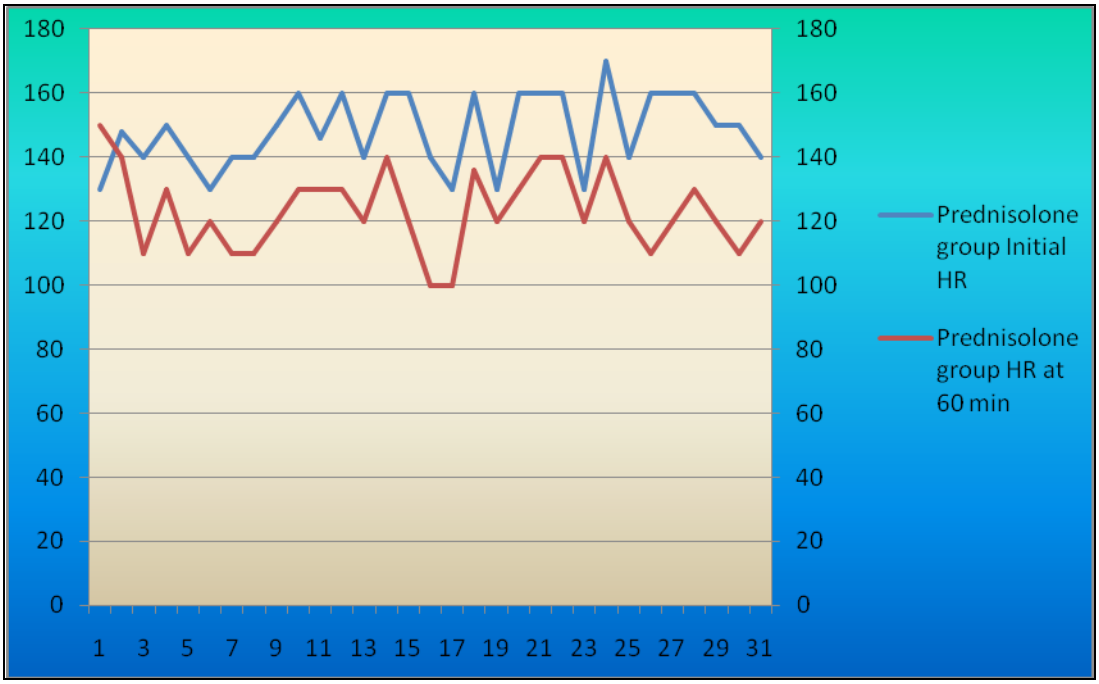
The average initial heart rate for budesonide group was 143.53 ± 11.66 which decreased significantly to an average rate of 106.67 ± 9.94 at 60 min ($p< 0.001$) (see table 6).

Comparison analysis revealed that the decrease in HR in budesonide group (36.87 ± 10.86) was significantly greater than in prednisolone group (24.77 ± 13.0) ($p < 0.001$).

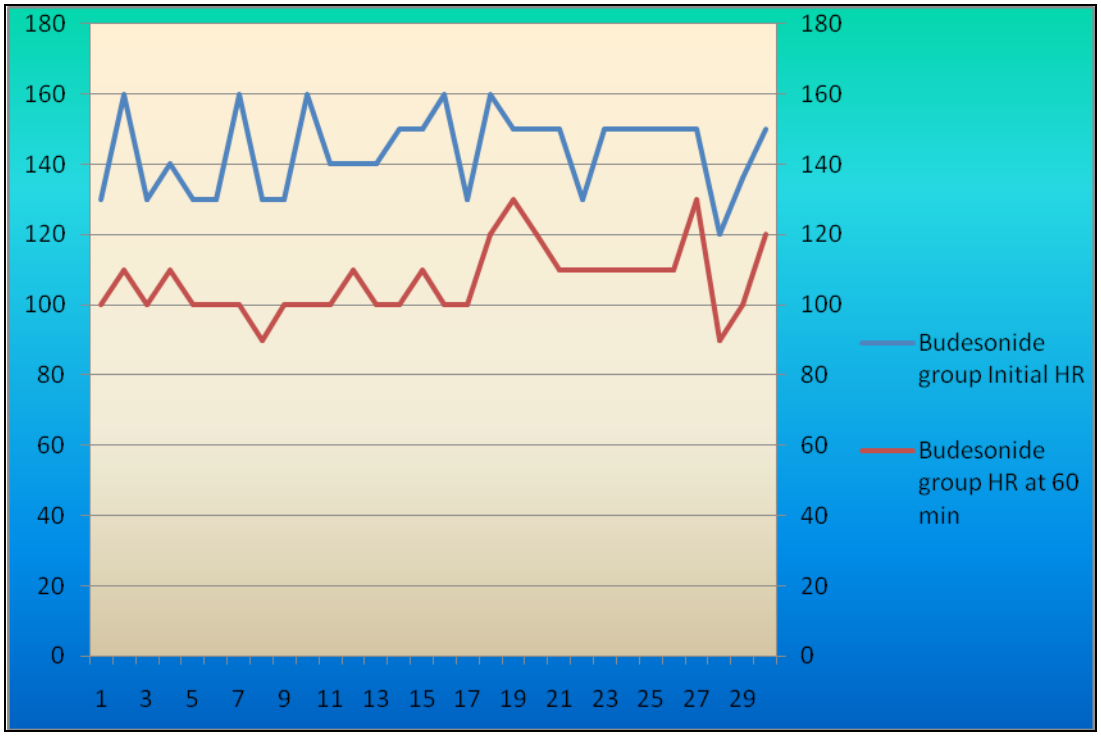
TABLE 6 Decrease in heart rate (HR) in prednisolone and budesonide groups

GROUP	AVERAGE INITIAL HR	AVERAGE HR AT 60 MIN	*p value*
Prednisolone group	148.2 ± 11.86	123.42 ± 12.64	< 0.001
Budesonide group	143.53 ± 11.66	106.67 ± 9.94	< 0.001

DECREASE IN HEART RATE IN PREDNISOLONE GROUP



DECREASE IN HEART RATE IN BUDESONIDE GROUP



Respiratory rate

Progressive decrease in respiratory rate was noted in both treatment groups. The average initial respiratory rate for prednisolone group was 53.80 ± 8.86 which showed a significant decrease after 1 hour of therapy to an average of 33.29 ± 9.63 ($p < 0.001$) (see table 7).

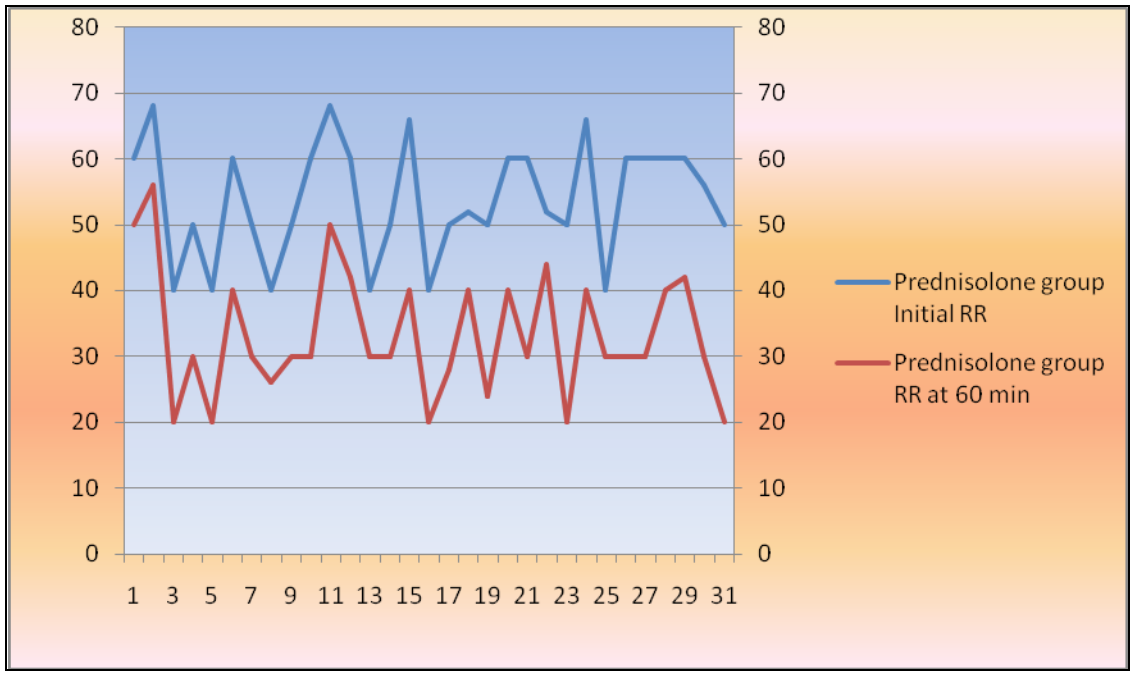
The average initial respiratory rate for budesonide group was 50.67 ± 6.02 which also decreased significantly to average rate of 28.60 ± 5.26 at 1 hour ($p < 0.001$) (see table 7).

But when comparing prednisolone group with budesonide group there was no significant difference in the decrease in respiratory rates noticed at 1 hr ($p > 0.2$).

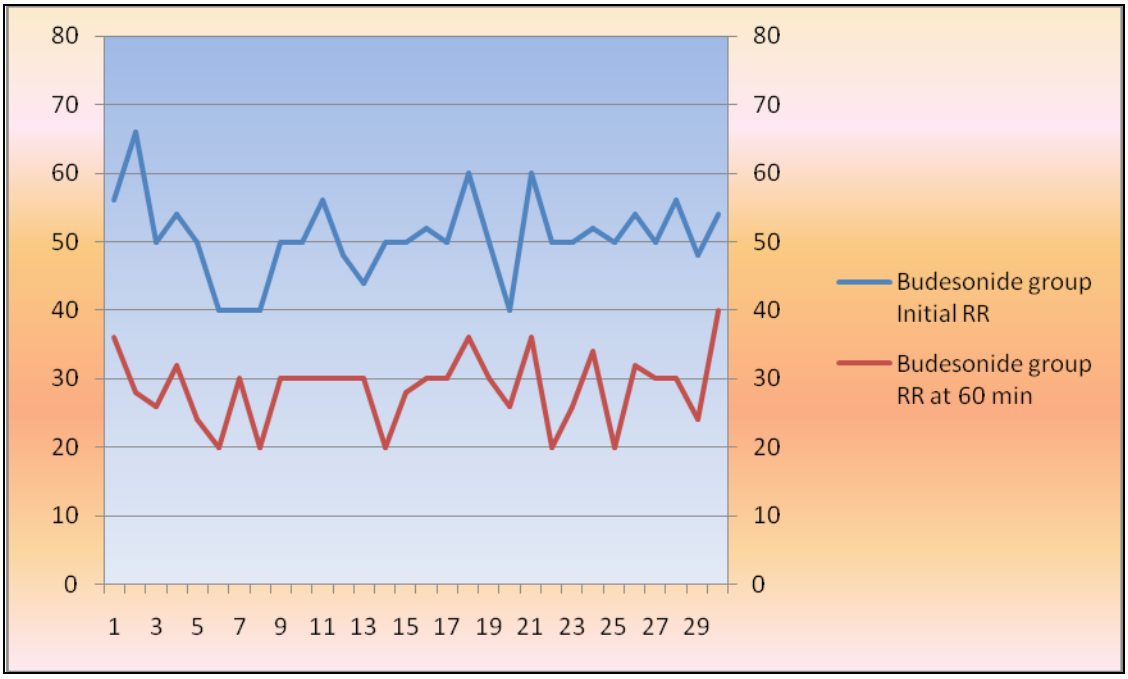
TABLE 7 Decrease in respiratory rate (RR) in prednisolone and budesonide groups

GROUP	AVERAGE INITIAL RR	AVERAGE RR AT 60 MIN	*p value*
Prednisolone group	53.80 ± 8.86	33.29 ± 9.63	< 0.001
Budesonide group	50.67 ± 6.02	28.60 ± 5.26	< 0.001

CHANGE IN RESPIRATORY RATE IN PREDNISOLONE GROUP



CHANGE IN RESPIRATORY RATE IN BUDESONIDE GROUP



Oxygen Saturation

Improvements in oxygen saturation were noted in both the groups. The average initial saturation was 98.39 ± 1.02 for prednisolone group. This value increased to an average of 99.84 ± 0.37at 1 hr which is statistically significant with a $p < 0.001$ (see table 8).

In budesonide group the average initial saturation noted was 98.37 ± 1.09 and this increased significantly to an average of 99.77 ± 0.43 ($p < 0.001$) (see table 8).

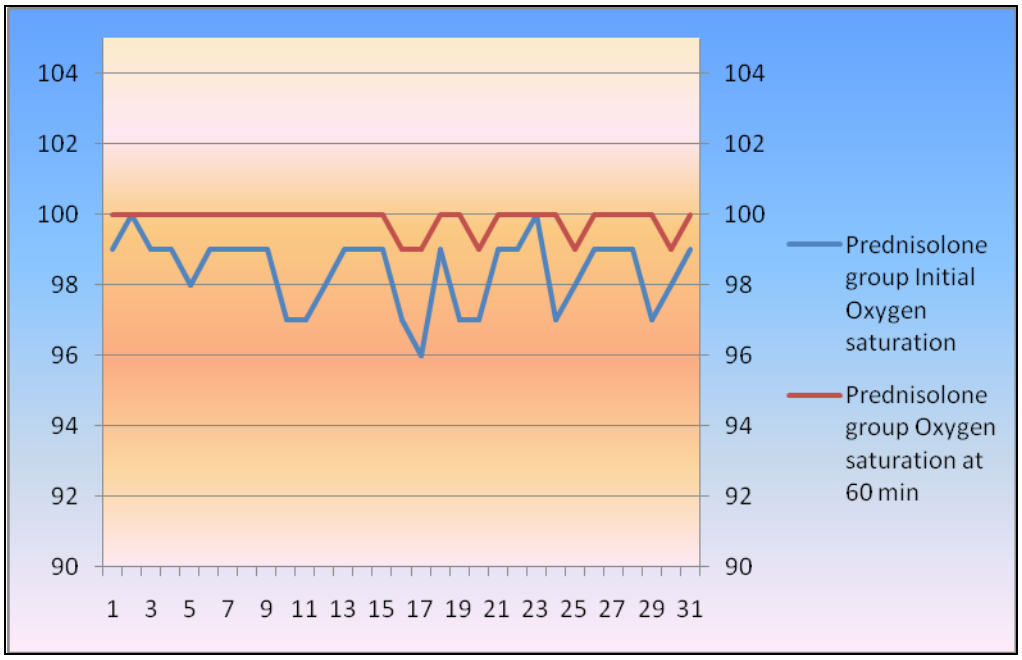
When comparing both the groups no significant difference in the improvement in saturation was noted ($p > 0.2$).

TABLE 8 Increase in Oxygen saturation in prednisolone and budesonide groups

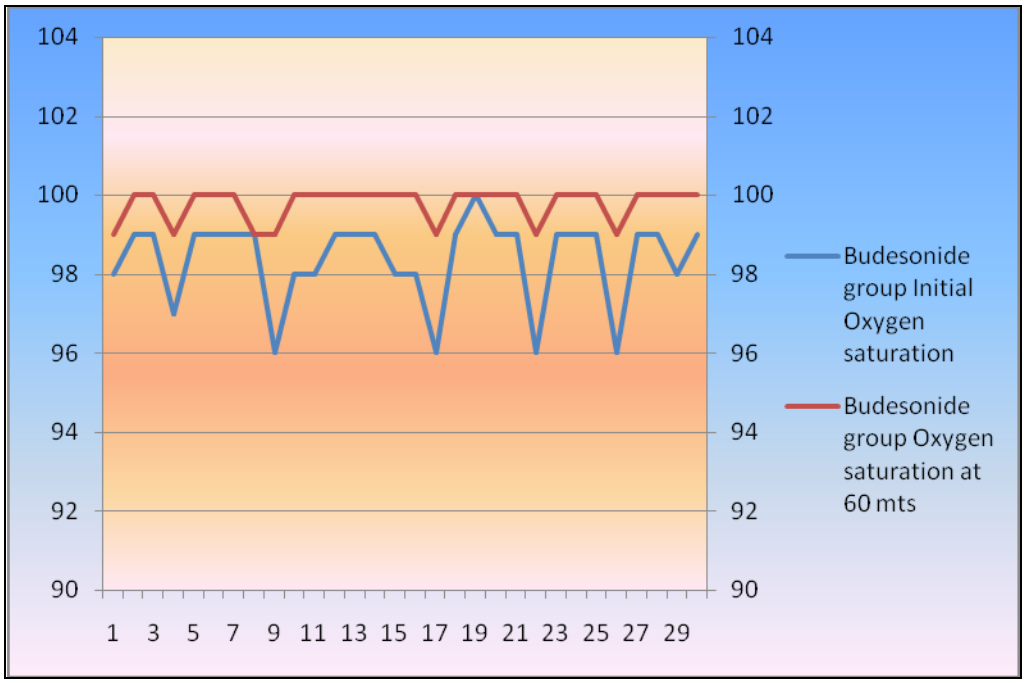
GROUP	AVERAGE INITIAL S_aO_2 *	AVERAGE S_aO_2 AT 60 MIN	*p value*
Prednisolone group	98.39 ± 1.02	99.84 ± 0.37	< 0.001
Budesonide group	98.37 ± 1.09	99.77 ± 0.43	< 0.001

* S_aO_2 – Oxygen saturation

MPROVEMENT IN OXYGEN SATURATION IN PREDNISOLONE GROUP



IMPROVEMENT IN OXYGEN SATURATION IN BUDESONIDE GROUP



Peak Expiratory Flow Rate

PEFR progressed differently in both the groups. The average initial PEFR was 185.88 ± 40.05 for prednisolone group and increased significantly to an average of 202.65 ± 35.93 at 4 hrs ($p < 0.001$) (see table 9).

Whereas, the average initial PEFR for budesonide group was 180.56 ± 38.15 and increased significantly to an average of 210.83 ± 30.79 at 4 hrs ($p < 0.001$) (see table 9).

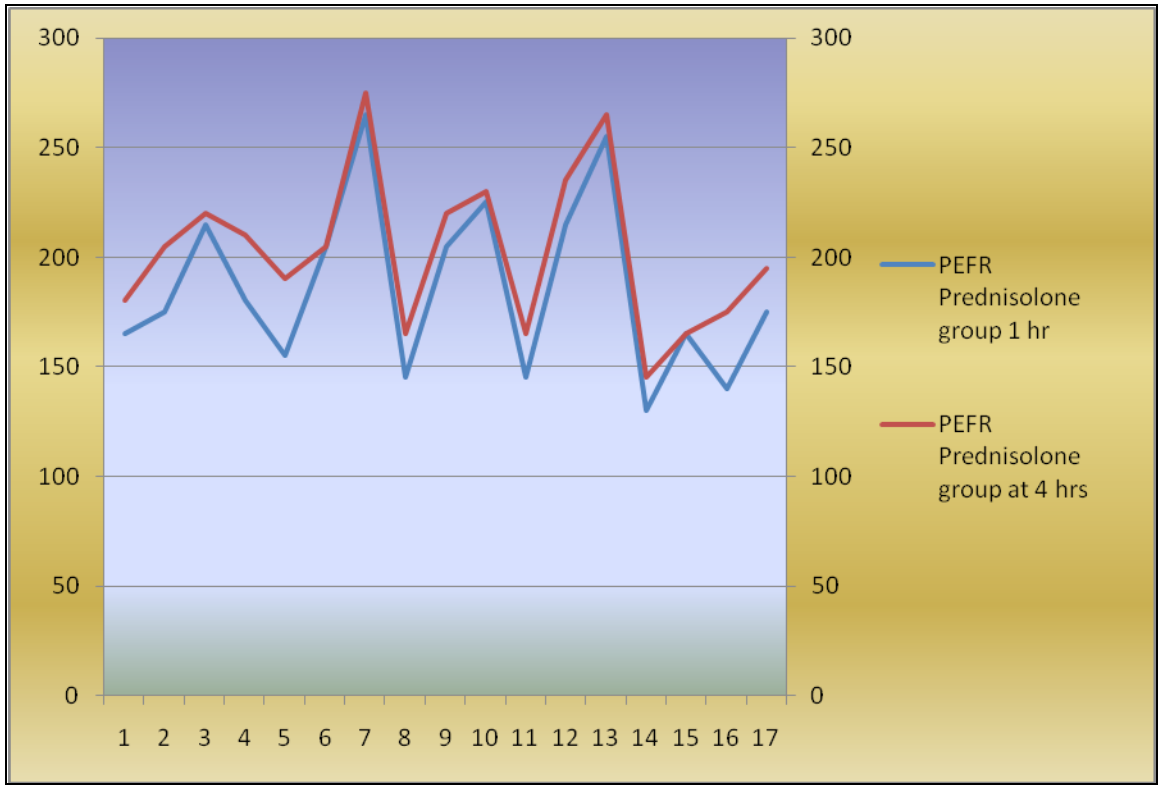
PEFR values showed greater improvement in budesonide group (30.28 ± 20.97) compared with prednisolone group (16.76 ± 11.17) which is significant with a p value <0.05.

TABLE 9 Improvement in PEFR* in prednisolone and budesonide groups

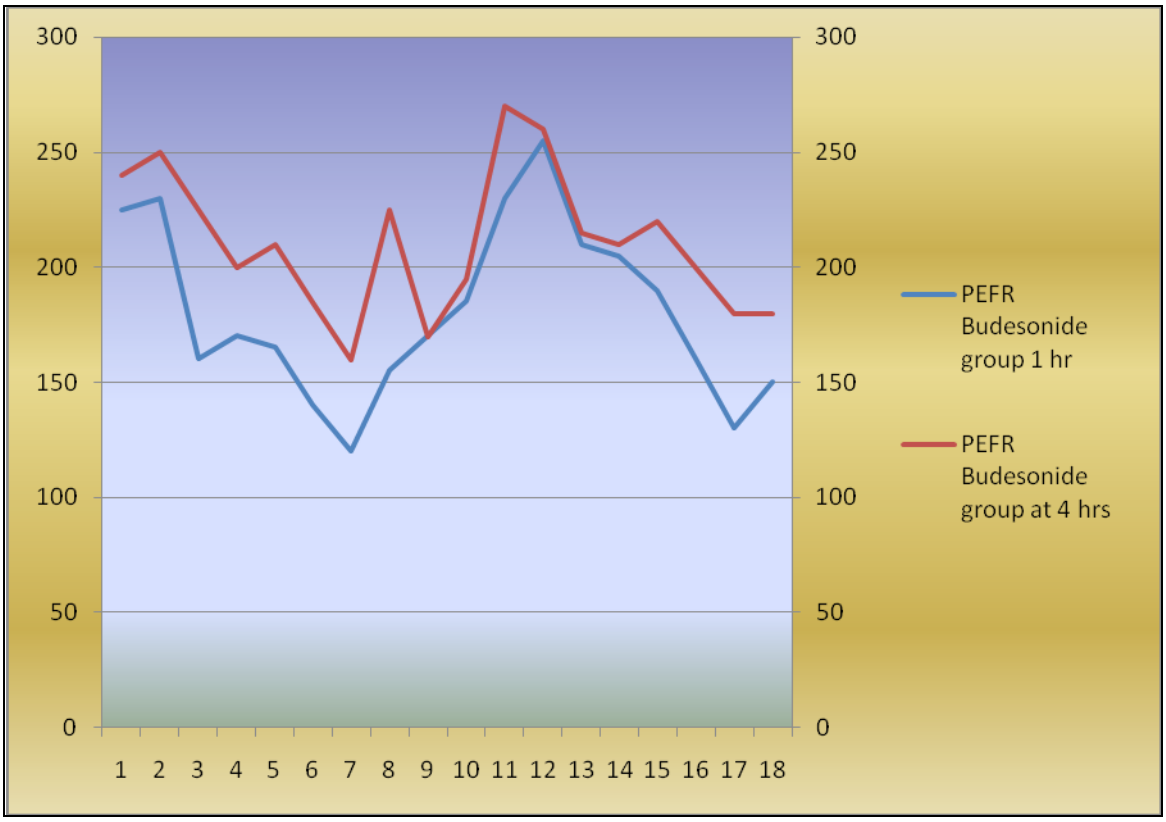
GROUP	AVERAGE PEFR AT I HR	AVERAGE PEFR* AT 4 HRS	*p value*
Prednisolone group	185.88 ± 40.0	202.65 ± 35.93	< 0.001
Budesonide group	180.56 ± 38.15	210.83 ± 30.79	< 0.001

* PEFR – Peak Expiratory Flow Rate

INCREMENT IN PEFR (PEAK EXPIRATORY FLOW RATE) IN PREDNISOLONE GROUP



INCREMENT IN PEFR IN BUDESONIDE GROUP



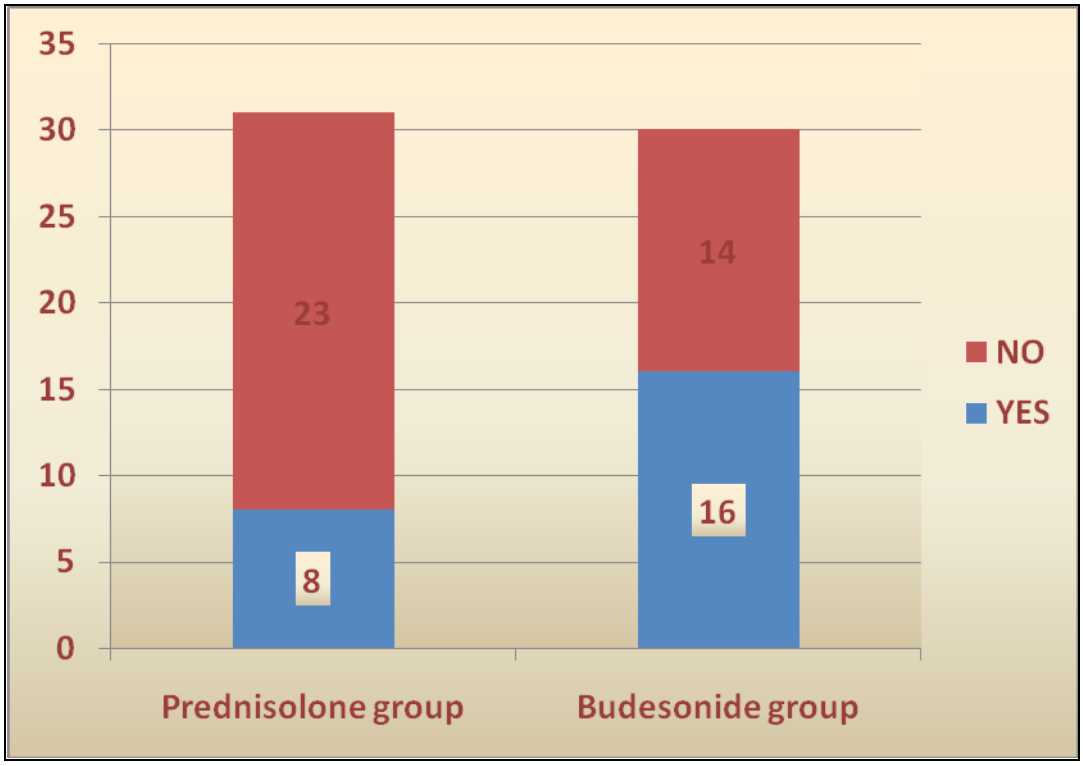
Fitness for discharge

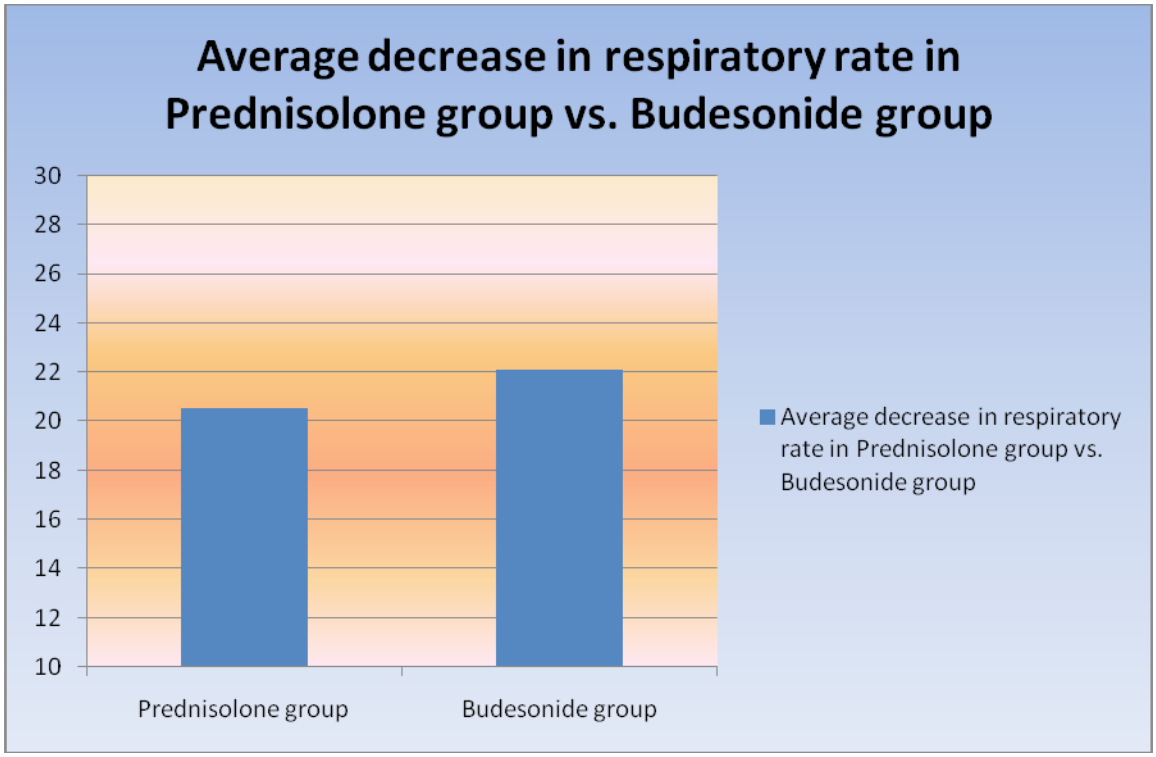
The fitness for discharge was based on the clinical severity scoring shown in table 2. The average baseline scores in both the groups were comparable ($p = 0.69$) as shown in table 5. Both groups showed a statistically significant improvement in clinical severity scores at the end of 2 hrs ($p < 0.001$).

A score of 0.4 or less is taken as criteria for discharge. Based on this scoring system, sixteen out of thirty patients in budesonide group (16/30, 53%) and eight out of thirty one patients in prednisolone group (8/31, 26%) were fit for discharge at the end of 2 hrs. The proportion of patients who were fit for discharge at the end of 2 h was significantly higher in budesonide group than in the prednisolone group (53% vs. 26%). This difference in *fitness for discharge rates* is statistically significant with a p value of < 0.05 (see table 10).

Table 10 Fitness for discharge in prednisolone group vs. budesonide group

GROUP	Fitness for discharge	
	YES	NO
Budesonide group	16	14
Prednisolone group	8	23





Adverse effects

No clinically significant adverse effects were noted in both the groups. Similarly, deterioration during management requiring discontinuation of the trial did not happen in both the groups. It therefore seems that both prednisolone and budesonide can be used safely in the management of acute exacerbation of asthma.

Table 11 Comparison in the outcome measures between the groups

Outcome measure	Prednisolone group	Budesonide group	*p* value

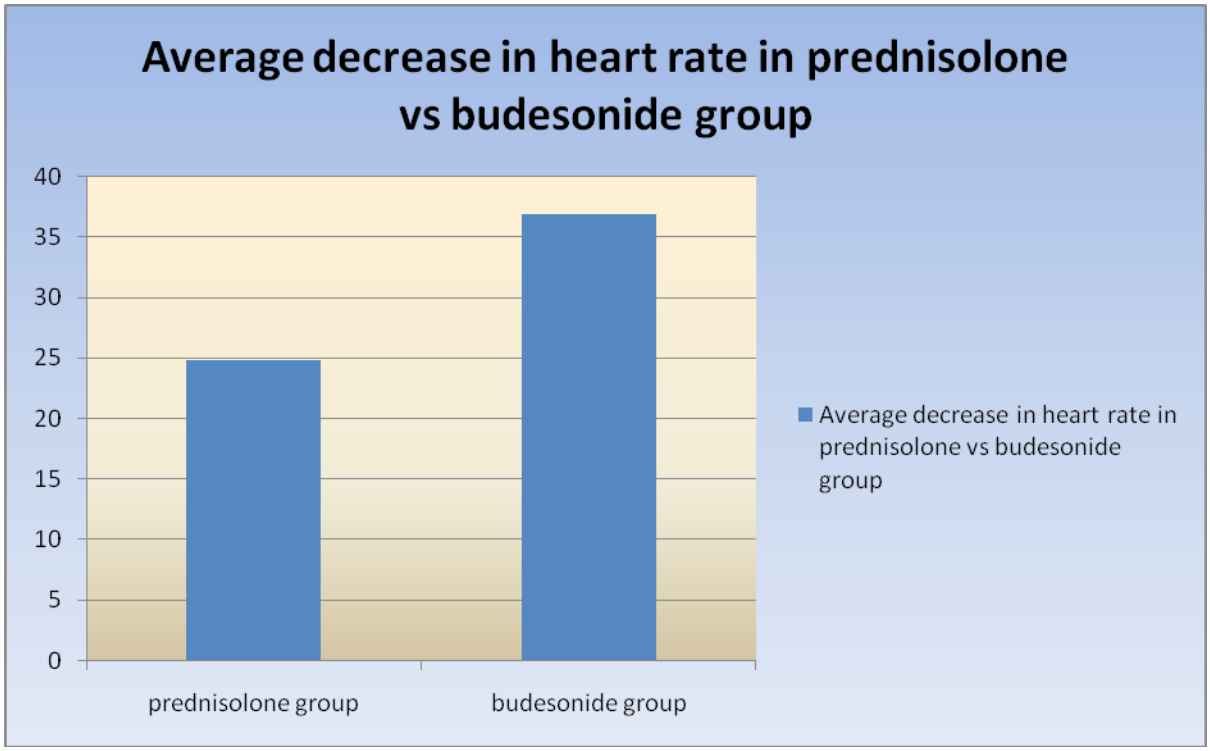
Decrease in Heart rate*	24.77 ± 13.0	36.87 ± 10.86	< 0.001
Decrease in Respiratory rate*	20.51 ± 6.73	22.07 ± 5.62	0.33
Improvement in Oxygen Saturation*	1.452 ±0.89	1.4 ± 0.81	0.81
Increment in PEFR[#]	16.76 ± 11.17	30.28 ± 20.97	< 0.05
Fitness for discharge[$]	53%	26%	< 0.05

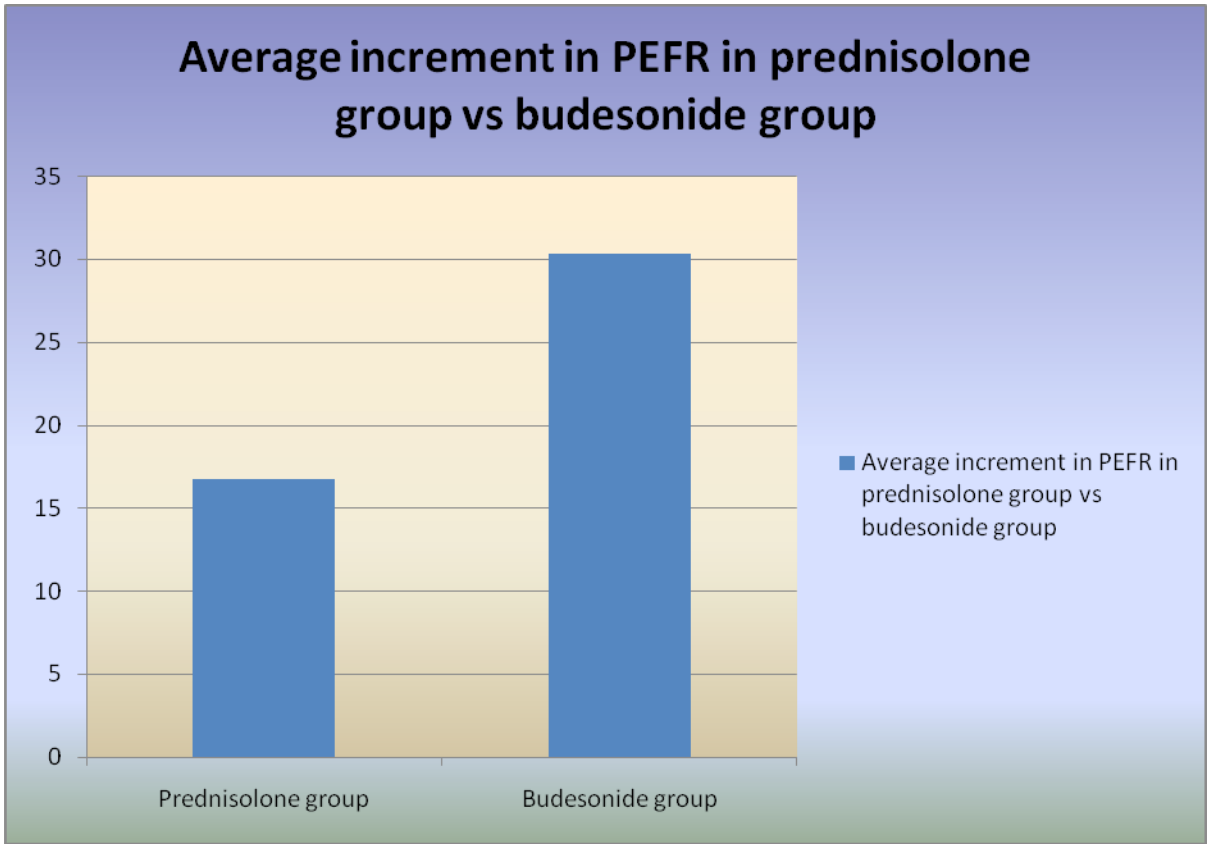
* at the end of 60 minutes

[#] at the end of 4 hrs

[$] at the end of 2 hrs

Children in budesonide group had greater decrease in heart rate compared with prednisolone group ($p < 0.001$). Similarly children in budesonide group also showed greater improvement in PEFR (peak expiratory flow rate) compared with prednisolone group ($p < 0.05$). But no statistically significant difference was noted between the groups with respect to change in respiratory rate and oxygen saturation. The proportion of patients who were fit for discharge at the end of 2 h was significantly higher in budesonide group than in the prednisolone group (53% vs. 26%), which is statistically significant with a p value < 0.05 (see table 11).


Average decrease in heart rate in prednisolone vs budesonide group
40
35
30
25
20
15
10
5
0
prednisolone group
budesonide group
Average decrease in heart rate in prednisolone vs budesonide group



MANAGEMENT OF ACUTE EXACERBATION OF ASTHMA IN THE EMERGENCY DEPARTMENT

\PEAK EXPIRATORY FLOW RATE MEASUREMENT IN A YOUNG CHILD

DISCUSSION

Inhaled glucocorticoid therapy is primarily used for asthma prophylaxis. Its use in acute exacerbation has not been fully evaluated because this form of glucocorticoid was believed to have minimal immediate activity. However, the rapid effect of nebulised budesonide has been demonstrated in both chronic and acute asthma. Several studies involving stable asthmatic patients showed improved spirometry within 1 hour of budesonide administration, with duration of effect between 5 and 12 hours.

The results revealed statistically significant improvement in vital signs (heart rate, respiratory rate), oxygen saturation, Peak Expiratory Flow rates (PEFR) and clinical scores in both the study

(budesonide) and control (prednisolone) groups at the end of treatment. There is also a significant increase in fitness for discharge rates at the end of 2 hrs in budesonide group compared with prednisolone group.

Comparison analysis showed significantly greater decrease in heart rate in budesonide group compared with prednisolone group at the end of treatment. Similarly statistically significant difference is peak expiratory flow rate increments between the study and control groups are noted at the end of 4 hrs. Children in budesonide group showed significantly greater improvement in PEFR compared with prednisolone group at the end of 4 hrs.

Children in both groups also had a significant decrease in respiratory rate at the end of three doses of nebulisation. However, no significant difference in improvement is noted between the groups. Hence it is concluded that both groups showed equal improvement with respect to decrease in respiratory rates.

Similarly oxygen saturation improved significantly at the end of treatment in both the prednisolone and budesonide groups. However, there is no significant difference in the improvement noted between the groups.

Both the treatment groups showed significant improvement in clinical scores at the end of two hours of treatment. Consequently *fitness for discharge rates* increased in both the groups. However, the *fitness for discharge rates* was significantly high in budesonide group compared with prednisolone group. This favours an early effect of high doses of inhaled budesonide at short intervals of 20 minutes on increasing the number of discharges.

The Number Needed to Treat (NNT) is calculated at 3.85 i.e. approximately 4, which means that 4 children are needed to be treated with nebulised budesonide to provide one additional clinical benefit i.e. one additional increase in discharge rate. This is a very relevant finding since hospital admissions count for the largest part of direct health costs for asthma.

Over the past decade, it has become increasingly recognized that airways inflammation is a major component of asthma. Due to their potent anti-inflammatory effects, therapy with systemic corticosteroids (oral, IM, or IV) is recommended in all patients presenting to the emergency department with an acute exacerbation of asthma. Furthermore, a short course of oral corticosteroids following emergency department discharge significantly reduces the number of relapses and the amount of ß-agonist use without an increase in side effects.

Many studies have suggested that the administration of parenteral corticosteroids (oral, IM, or IV) in addition to inhaled ß2-agonists in patients with acute asthma on their arrival at the emergency department neither improved airflow obstruction nor reduced the need for hospitalization. This effect may be due to the fact that it may take up to 24 h for the effects of corticosteroids to become evident.

In a meta-analysis preformed by Rodrigo and Rodrigo, involving seventeen randomised controlled trials, it has been shown that high doses of inhaled corticosteroids had rapid beneficial effects in improving pulmonary function thereby increasing early discharges.

They have shown that administration of high doses of inhaled corticosteroids together with salbutamol in patients with acute asthma who were treated in the emergency department significantly improved pulmonary function when compared to the use of salbutamol alone or a combination of

salbutamol with prednisolone.

Trials that used single doses of inhaled corticosteroids or multiple doses in very prolonged intervals presented smaller beneficial effects or no difference between the groups. So, the most important fact would not be the total dose administered, but rather the relationship between the dose and timing of administration. Hence the benefit is seen only when high doses are repeated at short intervals of less than 30 minutes. It is important to note that this benefit is evident within 90 min which may be helpful in early discharge thereby cutting down the costs of acute asthma management. It has been already suggested that locally acting (inhaled) corticosteroids act by causing local vasoconstriction and thereby decreasing edema formation and plasma exudation.

The economic cost of asthma is considerable both in terms of direct medical costs (such as hospital admissions and cost of pharmaceuticals) and indirect medical costs (such as time lost from work and premature death)[3]. It is therefore suggested that early use of inhaled corticosteroids in acute exacerbation of asthma may greatly reduce both the direct and indirect medical costs.

CONCLUSION

- Nebulised Budesonide has definite early clinical benefit in management of *Acute Severe Asthma*.

- Significant improvement in vital signs (decrease in heart rate and respiratory rate) and oxygen saturation were noted at the end of one hour of treatment with nebulised budesonide.

- Inhaled budesonide also improved pulmonary function as measured by Peak Expiatory Flow

Rate (PEFR) at the end of 4 hours of treatment.

- Inhaled Budesonide produced greater improvement in heart rate and pulmonary function (PEFR) compared with oral prednisolone.

- Though cost factor was not considered in the analysis, an overall view has shown that twice the numbers of children were fit for discharge in the Budesonide group when compared with Prednisolone group.

- This effect is particularly evident when high doses (800 μg) of inhaled Budesonide are administered along with inhaled β_2 agonists (salbutamol) and repeated at short intervals of 20 minutes for upto 3 doses.

RECOMMENDATION

Hence in a resource poor setting like ours, use of nebulised budesonide in the management of acute severe asthma is recommended as it produces favourable benefits by

- reducing the number of admissions
- reducing the social dislocation due to hospital admissions

- reducing the untoward side effects of prednisolone use
- reducing the costs for the patient and the hospital

DATA COLLECTION FORM

S. №: **Group:** **Date and time of arrival:**

Name: **Age:** **Sex:** **Weight:**

Name of parent: **Address:** **Height:**

S. №	Outcome measure	0 mts	20 mts	40 mts	60 mts	80 mts	4 hrs
1.	Respiratory rate						
2.	Heart rate						
3.	Oxygen saturation						

4.	**Peak expiratory flow rate**						
5.	**Clinical scoring**						
6.	**Clinical symptoms**						
7.	**Side effects**						

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